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IN THE UNITED SATES PATENT AND TRADEMARK OFFICE

In re:	U.S. Patent 5,776,456
Issued:	July 7, 1998
Inventors:	Darrel R. ANDERSON; Nabil HANNA; John E. LEONARD, Roland A. NEWMAN; Mitchell E. REFF; William H. RASTETTER
Assignee:	IDEC Pharmaceuticals Corporation
For:	THERAPEUTIC APPLICATION OF CHIMERIC AND RADIOLABELED ANTIBODIES TO HUMAN B LYMPHOCYTE RESTRICTED DIFFERENTIATION ANTIGEN FOR TREATMENT OF B CELL LYMPHOMA

Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

APPLICATION FOR EXTENSION OF PATENT TERM BASED ON REGULATORY REVIEW OF A NEW BIOLOGICS LICENSE APPLICATION AS PROVIDED UNDER 35 U.S.C. §156 (d)(1)

Sir:

Applicant, IDEC Pharmaceuticals Corporation, San Diego, California, hereby makes application under 35 U.S.C. §156(d)(1) and 37 C.F.R. §1.740 for extension of term of U.S. Patent 5,776,456, issued on July 7, 1998 based on an application filed June 7, 1995, which claims benefit of priority under 35 U.S.C. §120 to several U.S. patent applications, U.S. Serial No. 149,099 filed November 3, 1993 and U.S. Serial No. 978,891 filed November 13, 1992, abandoned.

The current expiration date of this patent is July 7, 2015, seventeen years from the aforementioned issue date.

The extension request is for a period of 227 days, or such greater or lesser period as the Commissioner may deem the applicant to be entitled. The extended expiration date of the patent

based on this extension period would be February 19, 2016, fourteen years from BLA approval. This is the maximum permitted extension provided for by 35 U.S.C. §156. The regulatory review period (reduced by one half of the IND period) is 1916 days and BLA review period is (475 days) (based on IND acceptance date of December 7, 1992, BLA acceptance date of December 29, 2000 and FDA approval letter for Zevalin™ dated February 19, 2002).

This application for extension is based on the regulatory approval of the Biologics License Application for Ibritumomab tiuxetan (Zevalin™), which comprises a radioimmuno-therapeutic for treatment of non-Hodgkin's lymphoma that comprises two radiolabeled anti-CD20 monoclonal antibodies filed under the provisions of §262 of Title 42, The Public Health and Welfare Act.

The active biologic ingredients in Zevalin™ include radiolabeled monoclonal antibodies:

(i) a mouse anti-human CD20 monoclonal antibody, 2B8 (Ibritumomab) which reacts with the CD20 antigen on human B-cells, conjugated via [N-[2bis(carboxy methyl) amino]- 3-(p-isothiocyanatophnyl)-propyl-[N-(2-bis(carboxymethyl) amino]- 2-(methyl)-ethyl] glycine, hereafter referred to as MX-DTPA, to yttrium [90], which is used for tumor therapy; and

(ii) the same mouse anti-human CD20 monoclonal antibody, 2B8 (Ibritumomab), also conjugated via the same linker-chelator to Indium –[111] which is used for tumor imaging.

The 2B8 antibody is a murine IgG1 Kappa monoclonal antibody. These radiolabeled monoclonal antibodies are used to treat non-Hodgkin's lymphoma, a form of B cell lymphoma which is associated with B cell containing tumor tissues that express the CD20 antigen.

These antibodies are administered during a therapeutic regimen that includes use of a chimeric anti-CD20 antibody (Rituximab) previously approved for therapeutic use for treatment of non-Hodgkin's lymphoma. This approval did not include the combined use of this chimeric anti-CD20 antibody in conjunction with radiolabeled anti-CD20 antibody as provided for in the Zevalin™ approved BLA.

The date of the approval of the BLA for Zevalin™ is February 19, 2002. Applicant believes that this the first permitted commercial marketing or use of the above identified radiolabeled anti-CD20 antibodies as a biologic for human therapeutic use. This application is being made within the sixty-day statutory period provided in 35 U.S.C. §156(d)(1).

In accordance with the provisions of 37 C.F.R. §1.740, application provides the following information:

(1) a complete identification of the approved product as by appropriate chemical and genetic name, physical structure or characteristics.

Applicant submits herewith as Exhibit A to this application the package insert for Zevalin™ as approved by the FDA. This insert contains the appropriate chemical and generic description, physical structure and characteristics for the In-111 radiolabeled 2B8 monoclonal antibody and the Y-90 radiolabeled monoclonal antibody that comprise the two active ingredients in Zevalin™.

(2) A complete identification of the Federal Statute including the applicable provision of law under which regulatory review occurred.

The approval for Zevalin™ was made by the Food and Drug Administration pursuant to §262 of Title 42, The Public Health and Welfare Act.

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.

The FDA approved for commercial marketing or use of Zevalin™ occurred on February 19, 2002 as set forth in a letter from the FDA, to the assignee of the patent, IDEC Pharmaceuticals Corporation. Applicant submits herewith a copy of this letter of authorization as Exhibit F.

(4) An identification of each active ingredient in the product and a statement that each such active ingredient has not been previously approved for commercial marketing or use under the Federal Food Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients) the use for which it was approved, and the provision of law under which it was approved.

The active ingredients in Zevalin™ include two radiolabeled anti-CD20 monoclonal antibodies (as described in the Zevalin™ package insert, Exhibit A) approved for use in treating non-Hodgkin's lymphoma. These two radiolabeled antibodies have not been previously approved for commercial marketing or use under the Federal Food Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) A statement that the application is being submitted within the sixty-day period permitted for submission pursuant to §1.720(f) and an identification of the date of the last day on which the application could be submitted.

This application is being submitted on or before April 19, 2002, the last day of the sixty-day period following the February 19, 2002 NDA approval date that is not a Saturday, Sunday or holiday, as provided in Title 35, U.S.C. 1.720 (f).

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.

This application for extension relates to U.S. patent 5,776,456 issued on July 7, 1998 which is based on an application Serial No. 476,275 filed June 7, 1995, which is in turn a divisional of Serial No. 149,099 filed November 3, 1993, which is in turn a continuation-in-part of Serial No. 978,891, filed November 13, 1992, abandoned. This patent is currently set to expire on July 7, 2015, seventeen years from the U.S. patent issue date. This patent is assigned to the applicant IDEC Pharmaceuticals Corporation, San Diego, California. The inventors are Darrell R. Anderson, John R. Leonard, Roland A. Newman, Mitchell E. Reff and William H. Rastetter.

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.

A copy of the patent for which an extension is being sought, including the entire specification (including claims) appears in Exhibit B.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.

The patent for which extension is being sought has not been the subject of any disclaimer, certificate of correction, or reexamination certificate. Exhibit C provides copies of maintenance fee receipts for maintenance fees paid in connection with the above application.

The first maintenance fee for this patent was due on January 7, 2001, three years and six months from the date of issuance of the patent. The second maintenance fee for this patent is due 7 years from issuance, or July 7, 2005.

(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable claim(s) are directed to those of the approved product.

The approved product includes two active ingredients, an In[111]radiolabeled (a Ball antibody lymphoma) and an Y[90] radiolabeled monoclonal antibody that binds CD20 which have been approved for treatment of non-Hodgkin's lymphoma. The applicable patent claims (of the '456 patent, claims 5 and 6) are directed to the use of the approved product for treatment of B cell lymphoma.

Patent Claim	*Relationship to the Approved Product*
5. A method for the treatment of B cell lymphoma comprising the steps of: 1) administering, at a first administration period, an immunologically active chimeric anti-CD20 antibody to a human, wherein said chimeric anti-CD20 antibody is derived from a transfectoma comprising anti-CD20 in TCAE 8 as deposited with the American Type Culture Collection as ATCC deposit number 69119; and 2) administering, at a second administration period, a radiolabeled anti-CD20 antibody to said human.	The approved Biological Product, Zevalin™, includes two radiolabeled anti-CD20 antibodies which are used for treatment of non-Hodgkin's lymphoma. These radiolabeled antibodies are administered in conjunction with a chimeric anti-CD20 antibody produced by transfectoma TCAE8 Rituxan™ (see page 3 of package insert of package insert et al.)

6. The method of claim **5** wherein said radiolabeled anti-CD20 antibody comprises a monoclonal antibody secreted from a hybridoma identified by American Type Culture Collection deposit number HB 11388.

The approved Biological Zevalin™ includes two radiolabeled monoclonal antibodies that bind CD20, wherein these monoclonal antibodies are each secreted by the hybridoma deposited with the American Type Culture collection under deposit number HB 11388, and are approved for use in treatment of non-Hodgkin's lymphoma, a type of B cell lymphoma.

(10) A statement beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period, particularly, for a patent claiming a human drug, antibiotic, or human biological product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number and the date on which the NDA was approved or the Product License issued.

For the BLA Approval of IDEC-Y2B8 Zevalin™(Ibritumomab tiuxetan) the following are the applicable dates:

Effective date for IND	December 7, 1992 (IND# 4850)
Initial Submission of BLA	November 1, 2000
FDA Approval for BLA	February 19, 2002 (BL# 1250190)

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

Exhibit D provides a brief description of significant activities undertaken by IDEC Pharmaceuticals Corporation during the regulatory review period for Zevalin™ and provides applicable dates for such activities.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined.

Applicant believes that it is entitled to an extension for U.S. patent 5,776,456, in accordance with the provisions of 35 U.S.C. §156. Applicant believes that the period of extension applicable to the patent is 227 days, based on the chronology set out in the Excel spreadsheet, provided as Exhibit E.

(13) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (see 37 C.F.R. §1.765).

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon the application for extension (see 37 C.F.R. §1.20(j)).

Applicant hereby encloses a check in the amount of the prescribed fee under 37 C.F.R. §1.20(j), $1,120. If for any reasons this payment is insufficient, applicant hereby authorizes that any deficiency may be charged to Deposit Account 03-3975.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.

Please direct all correspondence in connection with this application to:

Robin L. Teskin
PILLSBURY WINTHROP LLP
1600 Tysons Boulevard
McLean, Virginia 22102
Telephone: 703-905-2200

(16) An original of the application papers, certified as such and two copies are provided.

Applicant hereby certifies that this application for extension is being filed in triplicate (one original, two copies).

(17) An oath or declaration.

Applicant, through its undersigned patent attorney is authorized to practice before the Patent and Trademark Office and has general authority from the owner to act on behalf of the owner in patent matters, being duly warned that willful false statements are punishable by fine or imprisonment or both under section 1001 of Title 18, United States Code and that willful false

statements and the like may jeopardize the validity of this application and the patent to which it relates, states and declares that the following statements made based on his own knowledge are true and that all statements made on information and belief are believed to be true:

(1) The undersigned is registered to practice before the Patent and Trademark Office and is making this declaration as a patent attorney who has general authority to act on behalf of the applicant in patent matters.

(2) The undersigned has reviewed and understands the contents of the application being submitted pursuant to this section;

(3) The undersigned believes the patent is subject to extension pursuant to 37 C.F.R. §1.710;

(4) The undersigned believes an extension of the length claimed is justified under 35 U.S.C. §156 and the applicable regulations; and

(5) The undersigned believes the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. §1.740.

If this application for extension of patent term is held to be informal, applicant may seek to have the holdings reviewed by filing a petition with the required fee, as necessary, pursuant to 37 C.F.R. §§ 1.181, 1.182 or 1.183, as appropriate, within such time as may be set in any notice that the application has been held to be informal, or if no time is set, within one month of the date on which the application was held informal.

Applicant is providing herewith in Exhibit G a power of attorney and general authority for the undersigned to execute this application and make the declaration as provided in item (17) above.

Respectfully submitted,

IDEC Pharmaceuticals Corporation

Date: April 17, 2002 By: Samir Bhavsar Reg No 43,601

for Robin L. Teskin, Registration No.35,030
PILLSBURY WINTHROP LLP
1600 Tysons Boulevard
McLean, Virginia 22102
Telephone: (703) 905-2200
Facsimile (703) 905-2500

Attachments:

Check for $1,120.00

Exhibit A- Zevalin™ package insert as approved by the FDA.

Exhibit B- Copy of U.S. Patent 5,776,456.

Exhibit C- Copies of maintenance fee receipts.

Exhibit D- Description of significant activities undertaken during the regulatory review period for Zevalin™ and applicable dates for such activities.

Exhibit E- Excel spreadsheet containing calculation of period of extension.

Exhibit F- FDA Letter to IDEC Pharmaceuticals Corporation.

Exhibit G- Power of Attorney and General Authority from Assignee.

Exhibit A

Zevalin® Package Insert
as Approved by the FDA

A

Ibritumomab Tiuxetan

ZEVALIN™

Kits for the Preparation of Indium-111 (In–111) Ibritumomab Tiuxetan (In-111 ZEVALIN) and Yttrium–90 (Y–90) Ibritumomab Tiuxetan (Y-90 ZEVALIN)

In–111 Ibritumomab Tiuxetan and Y–90 Ibritumomab Tiuxetan are components of the ZEVALIN therapeutic regimen (See Description).

WARNINGS

Fatal Infusion Reactions: Deaths have occurred within 24 hours of Rituximab infusion, an essential component of the ZEVALIN therapeutic regimen. These fatalities were associated with an infusion reaction symptom complex that included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Approximately 80% of fatal infusion reactions occurred in association with the first Rituximab infusion (See WARNINGS and ADVERSE REACTIONS). Patients who develop severe infusion reactions should have Rituximab, In-111 ZEVALIN, and Y-90 ZEVALIN infusions discontinued and receive medical treatment.

Prolonged and Severe Cytopenias: Y-90 ZEVALIN administration results in severe and prolonged cytopenias in most patients. The ZEVALIN therapeutic regimen should not be administered to patients with ≥ 25% lymphoma marrow involvement and/or impaired bone marrow reserve (See ADVERSE REACTIONS and CLINICAL STUDIES).

Dosing

- The prescribed, measured, and administered dose of Y-90 ZEVALIN should not exceed the absolute maximum allowable dose of 32.0 mCi (1184 MBq).
- Y-90 ZEVALIN should not be administered to patients with altered biodistribution as determined by imaging with In-111 ZEVALIN.

In-111 ZEVALIN and Y-90 ZEVALIN are radiopharmaceuticals and should be used only by physicians and other professionals qualified by training and experienced in the safe use and handling of radionuclides.

DESCRIPTION

ZEVALIN™

ZEVALIN (Ibritumomab Tiuxetan) is the immunoconjugate resulting from a stable thiourea covalent bond between the monoclonal antibody Ibritumomab and the linker-chelator tiuxetan [N-[2-bis(carboxymethyl)amino]-3-(p-isothiocyanatophenyl)-

propyl]-[N-[2-bis(carboxymethyl)amino]-2-(methyl)-ethyl]glycine. This linker-chelator provides a high affinity, conformationally restricted chelation site for Indium-111 or Yttrium-90. The approximate molecular weight of Ibritumomab Tiuxetan is 148 kD.

The antibody moiety of ZEVALIN is Ibritumomab, a murine IgG_1 kappa monoclonal antibody directed against the CD20 antigen, which is found on the surface of normal and malignant B lymphocytes. Ibritumomab is produced in Chinese hamster ovary cells and is composed of two murine gamma 1 heavy chains of 445 amino acids each and two kappa light chains of 213 amino acids each.

ZEVALIN Therapeutic Regimen

The ZEVALIN therapeutic regimen is administered in two steps: Step 1 includes one infusion of Rituximab preceding In-111 ZEVALIN. Step 2 follows Step 1 by seven to nine days and consists of a second infusion of Rituximab followed by Y-90 ZEVALIN.

ZEVALIN is supplied as two separate and distinctly labeled kits that contain all of the non-radioactive ingredients necessary to produce a single dose of In-111 ZEVALIN and a single dose of Y-90 ZEVALIN, both essential components of the ZEVALIN therapeutic regimen. Indium-111 chloride and Rituximab must be ordered separately from the ZEVALIN kit. Yttrium-90 Chloride Sterile Solution is supplied by MDS Nordion when the Y-90 ZEVALIN kit is ordered.

ZEVALIN Kits

Each of the two ZEVALIN kits contains four vials that are used to produce a single dose of either In-111 ZEVALIN or Y-90 ZEVALIN, as indicated on the outer container label:

(1) One (1) ZEVALIN vial containing 3.2 mg of Ibritumomab Tiuxetan in 2 mL of 0.9% sodium chloride solution; a sterile, pyrogen-free, clear, colorless solution that may contain translucent particles; no preservative present.

(2) One (1) 50 mM Sodium Acetate Vial containing 13.6 mg of sodium acetate trihydrate in 2 mL of Water for Injection; a sterile, pyrogen-free, clear, colorless solution; no preservative present.

(3) One (1) Formulation Buffer Vial containing 750 mg of Albumin (Human), 76 mg of sodium chloride, 21 mg of sodium phosphate dibasic heptahydrate, 4 mg of pentetic acid, 2 mg of potassium phosphate monobasic and 2 mg of potassium chloride in 10 mL of Water for Injection adjusted to pH 7.1 with either sodium hydroxide or hydrochloric acid; a sterile, pyrogen-free, clear yellow to amber colored solution; no preservative present.

(4) One (1) empty Reaction Vial, sterile, pyrogen-free.

Physical/Radiochemical Characteristics of In-111

Indium-111 decays by electron capture, with a physical half-life of 67.3 hours (2.81 days).[1] The product of radioactive decay is nonradioactive cadmium-111. Radiation emission data for In-111 are summarized in Table 1.

Table 1.
Principal In-111 Radiation Emission Data

Radiation	Mean % per Disintegration	Mean Energy (keV)
Gamma-2	90.2	171.3
Gamma-3	94.0	245.4

External Radiation

The exposure rate constant for 37 MBq (1 mCi) of In-111 is 8.3 x 10^{-4} C/kg/hr (3.2 R/hr) at 1 cm. Adequate shielding should be used with this gamma-emitter, in accordance with institutional good radiation safety practices.

To allow correction for physical decay of In-111, the fractions that remain at selected intervals before and after the time of calibration are shown in Table 2.

Table 2.
Physical Decay Chart: In-111
Half-life 2.81 Days (67.3 Hours)

Calibration Time (Hrs.)	Fraction Remaining
-48	1.64
-42	1.54
-36	1.45
-24	1.28
-12	1.13
-6	1.06
0	1.00
6	0.94
12	0.88
24	0.78
36	0.69
42	0.65
48	0.61

Physical/Radiochemical Characteristics of Y-90

Yttrium-90 decays by emission of beta particles, with a physical half-life of 64.1 hours (2.67 days).[1] The product of radioactive decay is non-radioactive zirconium-90. The range of beta particles in soft tissue (χ_{90}) is 5 mm. Radiation emission data for Y-90 are summarized in Table 3.

Table 3.
Principal Y-90 Radiation Emission Data

Radiation	Mean % per Disintegration	Mean Energy (keV)
Beta minus	100	750-935

External Radiation

The exposure rate for 37 MBq (1 mCi) of Y-90 is 8.3 x 10^{-3} C/kg/hr (32 R/hr) at the mouth of an open Y-90 vial. Adequate shielding should be used with this beta-emitter, in accordance with institutional good radiation safety practices.

To allow correction for physical decay of Y-90, the fractions that remain at selected intervals before and after the time of calibration are shown in Table 4.

Table 4.
Physical Decay Chart: Y-90
Half-life 2.67 Days (64.1 Hours)

Calibration Time (Hrs.)	Fraction Remaining	Calibration Time (Hrs.)	Fraction Remaining
-36	1.48	0	1.00
-24	1.30	1	0.99
-12	1.14	2	0.98
-8	1.09	3	0.97
-7	1.08	4	0.96
-6	1.07	5	0.95
-5	1.06	6	0.94
-4	1.04	7	0.93
-3	1.03	8	0.92
-2	1.02	12	0.88
-1	1.01	24	0.77
0	1.00	36	0.68

CLINICAL PHARMACOLOGY

General Pharmacology

Ibritumomab Tiuxetan binds specifically to the CD20 antigen (human B-lymphocyte-restricted differentiation antigen, Bp35).[2, 3] The apparent affinity (K_D) of Ibritumomab Tiuxetan for the CD20 antigen ranges between approximately 14 to 18 nM. The CD20 antigen is expressed on pre-B and mature B lymphocytes and on > 90% of B-cell non-Hodgkin's lymphomas (NHL).[4, 5] The CD20 antigen is not shed from the cell surface and does not internalize upon antibody binding.[6]

Mechanism of Action: The complementarity-determining regions of Ibritumomab bind to the CD20 antigen on B lymphocytes. Ibritumomab, like Rituximab, induces apoptosis in CD20+ B-cell lines *in vitro*.[6] The chelate tiuxetan, which tightly binds In-111 or

Y-90, is covalently linked to the amino groups of exposed lysines and arginines contained within the antibody. The beta emission from Y-90 induces cellular damage by the formation of free radicals in the target and neighboring cells.[7]

Normal Human Tissue Cross-Reactivity: Ibritumomab Tiuxetan binding was observed *in vitro* on lymphoid cells of the bone marrow, lymph node, thymus, red and white pulp of the spleen, and lymphoid follicles of the tonsil, as well as lymphoid nodules of other organs such as the large and small intestines. Binding was not observed on the nonlymphoid tissues or gonadal tissues (see **CLINICAL PHARMACOLOGY, Radiation Dosimetry**)

Pharmacokinetics / Pharmacodynamics

Pharmacokinetic and biodistribution studies were performed using In-111 ZEVALIN (5 mCi [185 MBq] In-111, 1.6 mg Ibritumomab Tiuxetan). In a study designed to assess the need for pre-administration of unlabeled antibody, only 18% of known sites of disease were imaged when In-111 ZEVALIN was administered without unlabeled Ibritumomab. When preceded by unlabeled Ibritumomab (1.0 mg/kg or 2.5 mg/kg), In-111 ZEVALIN detected 56% and 92% of known disease sites, respectively.

In pharmacokinetic studies of patients receiving the ZEVALIN therapeutic regimen, the mean effective half-life for Y-90 activity in blood was 30 hours, and the mean area under the fraction of injected activity (FIA) vs. time curve in blood was 39 hours. Over 7 days, a median of 7.2% of the injected activity was excreted in urine.

In clinical studies, administration of the ZEVALIN therapeutic regimen resulted in sustained depletion of circulating B cells. At four weeks, the median number of circulating B cells was zero (range, 0-1084 cell/mm^3). B-cell recovery began at approximately 12 weeks following treatment, and the median level of B cells was within the normal range (32 to 341 cells/mm^3) by 9 months after treatment. Median serum levels of IgG and IgA remained within the normal range throughout the period of B-cell

depletion. Median IgM serum levels dropped below normal (median 49 mg/dL, range 13-3990 mg/dL) after treatment and recovered to normal values by 6-month post therapy.

Radiation Dosimetry

Estimations of radiation-absorbed doses for In-111 ZEVALIN and Y-90 ZEVALIN were performed using sequential whole body images and the MIRDOSE 3 software program.[8, 9] The estimated radiation absorbed doses to organs and marrow from a course of the ZEVALIN therapeutic regimen are summarized in Table 5. Absorbed dose estimates for the lower large intestine, upper large intestine, and small intestine have been modified from the standard MIRDOSE 3 output to account for the assumption that activity is within the intestine wall rather than the intestine contents.

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138 **Table 5.**

139 **Estimated Radiation Absorbed Doses From Y-90 ZEVALIN and In-111 ZEVALIN**

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Organ	Y-90 ZEVALIN mGy/MBq		In-111 ZEVALIN mGy/MBq	
	Median	**Range**	**Median**	**Range**
Spleen[1]	9.4	1.8 - 14.4	0.9	0.2 - 1.2
Testes[1]	9.1	5.4 - 11.4	0.6	0.4 - 0.8
Liver[1]	4.8	2.3 - 8.1	0.7	0.3 - 1.1
Lower Large Intestinal Wall[1]	4.8	3.1 – 8.2	0.4	0.2 - 0.6
Upper Large Intestinal Wall[1]	3.6	2.0 – 6.7	0.3	0.2 - 0.6
Heart Wall[1]	2.8	1.5 - 3.2	0.4	0.2 - 0.5
Lungs[1]	2.0	1.2 - 3.4	0.2	0.1 - 0.4
Small Intestine[1]	1.4	0.8 – 2.1	0.2	0.1 - 0.3
Red Marrow[2]	1.3	0.7 - 1.8	0.2	0.1 - 0.2
Urinary Bladder Wall[3]	0.9	0.7 - 2.1	0.2	0.1 - 0.2
Bone Surfaces[2]	0.9	0.5 - 1.2	0.2	0.1 - 0.2
Ovaries[3]	0.4	0.3 - 0.5	0.2	0.2 - 0.2
Uterus[3]	0.4	0.3 - 0.5	0.2	0.1 - 0.2
Adrenals[3]	0.3	0.0 - 0.5	0.2	0.1 - 0.3
Brain[3]	0.3	0.0 - 0.5	0.1	0.0 - 0.1
Breasts[3]	0.3	0.0 - 0.5	0.1	0.0 - 0.1
Gallbladder Wall[3]	0.3	0.0 - 0.5	0.3	0.1 - 0.4
Muscle[3]	0.3	0.0 - 0.5	0.1	0.0 - 0.1
Pancreas[3]	0.3	0.0 - 0.5	0.2	0.1 - 0.3
Skin[3]	0.3	0.0 - 0.5	0.1	0.0 - 0.1
Stomach[3]	0.3	0.0 - 0.5	0.1	0.1 - 0.2
Thymus[3]	0.3	0.0 - 0.5	0.1	0.1 - 0.2
Thyroid[3]	0.3	0.0 - 0.5	0.1	0.0 - 0.1
Kidneys[1]	0.1	0.0 - 0.2	0.2	0.1 - 0.2
Total Body[3]	0.5	0.2 - 0.7	0.1	0.1 - 0.2

141 1 Organ region of interest
142 2 Sacrum region of interest [10]
143 3 Whole body region of interest
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CLINICAL STUDIES

The safety and efficacy of the ZEVALIN therapeutic regimen were evaluated in two multi-center trials enrolling a total of 197 subjects. The ZEVALIN therapeutic regimen was administered in two steps (see DOSAGE AND ADMINISTRATION). The activity and toxicity of a variation of the ZEVALIN therapeutic regimen employing a reduced dose of Y-90 ZEVALIN was further defined in a third study enrolling a total of 30 patients who had mild thrombocytopenia (platelet count 100,000 to 149,000 cells/mm^3).

Study 1 was a single arm study of 54 patients with relapsed follicular lymphoma refractory to Rituximab treatment. Patients were considered refractory if their last prior treatment with Rituximab did not result in a complete or partial response, or if time to disease progression (TTP) was < 6 months. The primary efficacy endpoint of the study was the overall response rate (ORR) using the International Workshop Response Criteria (IWRC).[11] Secondary efficacy endpoints included time to disease progression (TTP) and duration of response (DR). In a secondary analysis comparing objective response to the ZEVALIN therapeutic regimen with that observed with the most recent treatment with Rituximab, the median duration of response following the ZEVALIN therapeutic regimen was 6 vs. 4 months. Table 6 summarizes efficacy data from this study.

Study 2 was a randomized, controlled, multicenter study comparing the ZEVALIN therapeutic regimen to treatment with Rituximab. The trial was conducted in 143 patients with relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma (NHL), or transformed B-cell NHL. A total of 73 patients received the ZEVALIN therapeutic regimen, and 70 patients received Rituximab given as an IV infusion at 375 mg/m^2 weekly times 4 doses. The primary efficacy endpoint of the study was to determine the ORR using the IWRC[11] (see Table 6). The ORR was significantly higher (80% vs. 56%, $p = 0.002$) for patients treated with the ZEVALIN therapeutic regimen. The secondary endpoints, duration of response and time to progression, were not significantly different between the two treatment arms.

Table 6.
Summary of Efficacy Data[1]

	Study 1	Study 2	
	ZEVALIN therapeutic regimen N = 54	**ZEVALIN therapeutic regimen N = 73**	**Rituximab N = 70**
Overall Response Rate (%)	74	80	56
Complete Response Rate (%)	15	30	16
CRu Rate[2] (%)	0	4	4
Median DR[3,4] (Months) [Range[5]]	6.4 [0.5-24.9+]	13.9 [1.0-30.1+]	11.8 [1.2-24.5]
Median TTP[3,6] (Months) [Range[5]]	6.8 [1.1-25.9+]	11.2 [0.8-31.5+]	10.1 [0.7-26.1]

[1]IWRC: International Workshop response criteria
[2]CRu: Unconfirmed complete response
[3]Estimated with observed range.
[4]Duration of response: interval from the onset of response to disease progression.
[5]"+" indicates an ongoing response.
[6]Time to Disease Progression: interval from the first infusion to disease progression.

Study 3 was a single arm study of 30 patients with relapsed or refractory low-grade, follicular, or transformed B-cell NHL who had mild thrombocytopenia (platelet count 100,000 to 149,000 cells/mm^3). Excluded from the study were patients with ≥ 25% lymphoma marrow involvement and/or impaired bone marrow reserve. Patients were considered to have impaired bone marrow reserve if they had any of the following: prior myeloablative therapy with stem cell support; prior external beam radiation to > 25% of active marrow; a platelet count <100,000 cells/mm^3; or neutrophil count <1,500 cells/mm^3. In this study, a modification of the ZEVALIN therapeutic regimen with a lower specific activity Y-90 ZEVALIN dose [(Y-90 ZEVALIN at 0.3 mCi/kg (11.1 MBq/kg)] was used. Objective, durable clinical responses were observed [67% ORR (95% CI: 48-85%), 11.8 months median DR (range: 4-17 months)] and resulted in a greater incidence of hematologic toxicity (see ADVERSE REACTIONS) than in Studies 1 and 2.

INDICATIONS AND USAGE

ZEVALIN, as part of the ZEVALIN therapeutic regimen (see DOSAGE AND ADMINISTRATION), is indicated for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma,

including patients with Rituximab refractory follicular non-Hodgkin's lymphoma. Determination of the effectiveness of the ZEVALIN therapeutic regimen in a relapsed or refractory patient population is based on overall response rates (see CLINICAL STUDIES). The effects of the ZEVALIN therapeutic regimen on survival are not known.

CONTRAINDICATIONS

The ZEVALIN therapeutic regimen is contraindicated in patients with known Type I hypersensitivity or anaphylactic reactions to murine proteins or to any component of this product, including Rituximab, yttrium chloride, and indium chloride.

WARNINGS (SEE BOXED WARNING)

Altered Biodistribution: Y-90 ZEVALIN should not be administered to patients with altered biodistribution of In-111 ZEVALIN. The expected biodistribution of In-111 ZEVALIN includes easily detectable uptake in the blood pool areas on the first day image, with less activity in the blood pool areas on the second or third day image; moderately high to high uptake in normal liver and spleen during the first day and the second or third day image; and moderately low or very low uptake in normal kidneys, urinary bladder, and normal bowel on the first day image and the second or third day image. Altered biodistribution of In-111 ZEVALIN can be characterized by diffuse uptake in normal lung more intense than the cardiac blood pool on the first day image or more intense than the liver on the second or third day image; kidneys with greater intensity than the liver on the posterior view of the second or third day image; or intense areas of uptake throughout the normal bowel comparable to uptake by the liver on the second or third day images.

Severe Infusion Reactions (See PRECAUTIONS, Hypersensitivity): The ZEVALIN therapeutic regimen may cause severe, and potentially fatal, infusion reactions. These severe reactions typically occur during the first Rituximab infusion with time to onset of 30 to 120 minutes. Signs and symptoms of severe infusion reaction may include hypotension, angioedema, hypoxia, or bronchospasm, and may require interruption of Rituximab, In-111 ZEVALIN, or Y-90 ZEVALIN administration. The most severe

manifestations and sequelae may include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. **Because the ZEVALIN therapeutic regimen includes the use of Rituximab, see also prescribing information for RITUXAN (Rituximab).**

Cytopenias (See ADVERSE REACTIONS, Hematologic Events):

The most common severe adverse events reported with the ZEVALIN therapeutic regimen were thrombocytopenia (61% of patients with platelet counts <50,000 cells/mm^3) and neutropenia (57% of patients with absolute neutrophil count (ANC) <1,000 cells/mm^3) in patients with ≥150,000 platelets/mm^3 prior to treatment. Both incidences of severe thrombocytopenia and neutropenia increased to 78% and 74% for patients with mild thrombocytopenia at baseline (platelet count of 100,000 to 149,000 cells/mm^3). For all patients, the median time to nadir was 7-9 weeks and the median duration of cytopenias was 22-35 days. In <5% of cases, patients experienced severe cytopenia that extended beyond the prospectively defined protocol treatment period of 12 weeks following administration of the ZEVALIN therapeutic regimen. Some of these patients eventually recovered from cytopenia, while others experienced progressive disease, received further anti-cancer therapy, or died of their lymphoma without having recovered from cytopenia. The cytopenias may have influenced subsequent treatment decisions.

Hemorrhage, including fatal cerebral hemorrhage, and severe infections have occurred in a minority of patients in clinical studies. Careful monitoring for and management of cytopenias and their complications (e.g., febrile neutropenia, hemorrhage) for up to 3 months after use of the ZEVALIN therapeutic regimen are necessary. Caution should be exercised in treating patients with drugs that interfere with platelet function or coagulation following the ZEVALIN therapeutic regimen and patients receiving such agents should be closely monitored.

The ZEVALIN therapeutic regimen should not be administered to patients with ≥ 25% lymphoma marrow involvement and/or impaired bone marrow reserve, e.g., prior

myeloablative therapies; platelet count <100,000 cells/mm^3; neutrophil count <1,500 cells/mm^3; hypocellular bone marrow (≤15% cellularity or marked reduction in bone marrow precursors); or to patients with a history of failed stem cell collection.

Secondary Malignancies: Out of 349 patients treated with the ZEVALIN therapeutic regimen, three cases of acute myelogenous leukemia and two cases of myelodysplastic syndrome have been reported following the ZEVALIN therapeutic regimen (see ADVERSE REACTIONS).

Pregnancy Category D: Y-90 ZEVALIN can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Creutzfeldt-Jakob disease (CJD): This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS

The ZEVALIN therapeutic regimen is intended as a single course treatment. The safety and toxicity profile from multiple courses of the ZEVALIN therapeutic regimen or of other forms of therapeutic irradiation preceding, following, or in combination with the ZEVALIN therapeutic regimen have not been established.

Radionuclide Precautions: The contents of the ZEVALIN kit are not radioactive. However, during and after radiolabeling ZEVALIN with In-111 or Y-90, care should be taken to minimize radiation exposure to patients and to medical personnel, consistent with institutional good radiation safety practices and patient management procedures.

Hypersensitivity: Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. Medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines and corticosteroids, should be available for immediate use in the event of an allergic reaction during administration of ZEVALIN. Patients who have received murine proteins should be screened for human anti-mouse antibodies (HAMA). Patients with evidence of HAMA have not been studied and may be at increased risk of allergic or serious hypersensitivity reactions during ZEVALIN therapeutic regimen administrations.

Immunization: The safety of immunization with live viral vaccines following the ZEVALIN therapeutic regimen has not been studied. Also, the ability of patients who received the ZEVALIN therapeutic regimen to generate a primary or anamnestic humoral response to any vaccine has not been studied.

Laboratory Monitoring: Complete blood counts (CBC) and platelet counts should be obtained weekly following the ZEVALIN therapeutic regimen and should continue until levels recover. CBC and platelet counts should be monitored more frequently in patients who develop severe cytopenia, or as clinically indicated.

Drug Interactions: No formal drug interaction studies have been performed with ZEVALIN. Due to the frequent occurrence of severe and prolonged thrombocytopenia, the potential benefits of medications which interfere with platelet function and/or anticoagulation should be weighed against the potential increased risks of bleeding and hemorrhage. Patients receiving medications that interfere with platelet function or coagulation should have more frequent laboratory monitoring for thrombocytopenia. In addition, the transfusion practices for such patients may need to be modified given the increased risk of bleeding.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of the

ZEVALIN therapeutic regimen, or to determine its effects on fertility in males or females. However, radiation is a potential carcinogen and mutagen. The ZEVALIN therapeutic regimen results in a significant radiation dose to the testes. The radiation dose to the ovaries has not been established. There have been no studies to evaluate whether the ZEVALIN therapeutic regimen causes hypogonadism, premature menopause, azoospermia and/or mutagenic alterations to germ cells. There is a potential risk that the ZEVALIN therapeutic regimen could cause toxic effects on the male and female gonads. Effective contraceptive methods should be used during treatment and for up to 12 months following the ZEVALIN therapeutic regimen.

Pregnancy Category D: SEE WARNINGS.

Nursing Mothers: It is not known whether ZEVALIN is excreted in human milk. Because human IgG is excreted in human milk and the potential for ZEVALIN exposure in the infant is unknown, women should be advised to discontinue nursing and formula feeding should be substituted for breast feedings (see CLINICAL PHARMACOLOGY).

Geriatric Use: Of 349 patients treated with the ZEVALIN therapeutic regimen in clinical studies, 38% (132 patients) were age 65 years and over, while 12% (41 patients) were age 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Pediatric Use: The safety and effectiveness of the ZEVALIN therapeutic regimen in children have not been established.

ADVERSE REACTIONS

Safety data, except where indicated, are based upon 349 patients treated in 5 clinical studies with the ZEVALIN therapeutic regimen (see DOSAGE AND ADMINISTRATION). Because the ZEVALIN therapeutic regimen includes the use of Rituximab, also see prescribing information for RITUXAN (Rituximab).

The most serious adverse reactions caused by the ZEVALIN therapeutic regimen include infections (predominantly bacterial in origin), allergic reactions (bronchospasm and angioedema), and hemorrhage while thrombocytopenic (resulting in deaths). In addition, patients who have received the ZEVALIN therapeutic regimen have developed myeloid malignancies and dysplasias. Fatal infusion reactions have occurred following the infusion of Rituximab. Please refer to the BOXED WARNINGS and WARNINGS sections for detailed descriptions of these reactions.

The most common toxicities reported were neutropenia, thrombocytopenia, anemia, gastrointestinal symptoms (nausea, vomiting, abdominal pain, and diarrhea), increased cough, dyspnea, dizziness, arthralgia, anorexia, anxiety, and ecchymosis. Hematologic toxicity was often severe and prolonged, whereas most non-hematologic toxicity was mild in severity. Table 7 lists adverse events that occurred in $\geq$ 5% of patients. A more detailed description of the incidence and duration of hematologic toxicities, according to baseline platelet count (as an indicator of bone marrow reserve) is provided in Table 8, Hematologic Toxicity.

Table 7.
Incidence of Adverse Events in ≥ 5 % of Patients Receiving the ZEVALIN therapeutic regimen [†]
(N = 349)

	All Grades %	Grade 3/4 %
Any Adverse Event	**99**	**89**
Body as a Whole	**80**	**12**
Asthenia	43	3
Infection	29	5
Chills	24	<1
Fever	17	1
Abdominal Pain	16	3
Pain	13	1
Headache	12	1
Throat Irritation	10	0
Back Pain	8	1
Flushing	6	0
Cardiovascular System	**17**	**3**
Hypotension	6	1
Digestive System	**48**	**3**
Nausea	31	1
Vomiting	12	0
Diarrhea	9	<1
Anorexia	8	0
Abdominal enlargement	5	0
Constipation	5	0
Hemic and Lymphatic System	**98**	**86**
Thrombocytopenia	95	63
Neutropenia	77	60
Anemia	61	17
Ecchymosis	7	<1
Metabolic and Nutritional Disorders	**23**	**3**
Peripheral Edema	8	1
Angioedema	5	<1
Musculoskeletal System	**18**	**1**
Arthralgia	7	1
Myalgia	7	<1
Nervous System	**27**	**2**
Dizziness	10	<1
Insomnia	5	0
Respiratory System	**36**	**3**
Dyspnea	14	2
Increased Cough	10	0
Rhinitis	6	0
Bronchospasm	5	0
Skin and Appendages	**28**	**1**
Pruritus	9	<1
Rash	8	<1
Special Senses	**7**	**<1**
Urogenital System	**6**	**<1**

[†] Adverse events were followed for a period of 12 weeks following the first Rituximab infusion of the ZEVALIN therapeutic regimen

Note: All adverse events are included, regardless of relationship.

The following adverse events (except for those noted in Table 7) occurred in between 1 and 4% of patients during the treatment period: urticaria (4%), anxiety (4%), dyspepsia (4%), sweats (4%), petechia (3%), epistaxis (3%), allergic reaction (2%), and melena (2%).

Severe or life-threatening adverse events occurred in 1-5% of patients (except for those noted in Table 7) consisted of pancytopenia (2%), allergic reaction (1%), gastrointestinal hemorrhage (1%), melena (1%), tumor pain (1%), and apnea (1%). The following severe or life threatening events occurred in <1% of patients: angioedema, tachycardia, urticaria, arthritis, lung edema, pulmonary embolus, encephalopathy, hematemesis, subdural hematoma, and vaginal hemorrhage.

Hematologic Events: Hematologic toxicity was the most frequently observed adverse event in clinical trials. Table 8 presents the incidence and duration of severe hematologic toxicity for patients with normal baseline platelet count ($\geq$ 150,000 cells/mm^3) treated with the ZEVALIN therapeutic regimen and patients with mild thrombocytopenia (platelet count 100,000 to 149,000 cells/mm^3) at baseline who were treated with a modified ZEVALIN therapeutic regimen that included a lower specific activity Y-90 ZEVALIN dose at 0.3 mCi/kg (11.1 MBq/kg).

Table 8.
Severe Hematologic Toxicity

	ZEVALIN therapeutic regimen using 0.4 mCi/kg Y-90 Dose (14.8 MBq/kg)	Modified ZEVALIN therapeutic regimen using 0.3 mCi/kg Y-90 dose (11.1 MBq/kg)
ANC		
Median nadir (cells/mm^3)	800	600
Per Patient Incidence ANC <1000 cells/mm^3	57%	74%
Per Patient Incidence ANC <500 cells/mm^3	30%	35%
Median Duration (Days)* ANC <1000 cells/mm^3	22	29
Platelets		
Median nadir (cells/mm^3)	41,000	24,000
Per Patient Incidence Platelets <50,000 cells/mm^3	61%	78%
Per Patient Incidence Platelets <10,000 cells/mm^3	10%	14%
Median Duration (Days)# Platelets <50,000 cells/mm^3	24	35

*Median duration of neutropenia for patients with ANC <1000 cells/mm^3 (Date from last laboratory value showing ANC ≥1000 cells/mm^3 to date of first laboratory value following nadir showing ANC ≥1000 cells/mm^3, censored at initiation of next treatment or death)

Median duration of thrombocytopenia for patients with platelets <50,000 cells/mm^3 (Date from last laboratory value showing platelet count ≥50,000 cells/mm^3 to date of first laboratory value following nadir showing platelet count ≥50,000 cells/mm^3, censored at initiation of next treatment or death)

Median time to ANC nadir was 62 days, to platelet nadir was 53 days, and to hemoglobin nadir was 68 days. Information on growth factor use and platelet transfusions is based on 211 patients for whom data were collected. Filgrastim was given to 13% of patients and erythropoietin to 8%. Platelet transfusions were given to 22% of patients and red blood cell transfusions to 20%.

Infectious Events: During the first 3 months after initiating the ZEVALIN therapeutic regimen, 29% of patients developed infections. Three percent of patients developed serious infections comprising urinary tract infection, febrile neutropenia, sepsis, pneumonia, cellulitis, colitis, diarrhea, osteomyelitis, and upper respiratory tract

infection. Life threatening infections were reported for 2% of patients that included sepsis, empyema, pneumonia, febrile neutropenia, fever, and biliary stent-associated cholangitis. During follow-up from 3 months to 4 years after the start of treatment with ZEVALIN, 6% of patients developed infections. Two percent of patients had serious infections comprising urinary tract infection, bacterial or viral pneumonia, febrile neutropenia, perihilar infiltrate, pericarditis, and intravenous drug-associated viral hepatitis. One percent of patients had life threatening infections that included bacterial pneumonia, respiratory disease, and sepsis.

Secondary Malignancies: A total of 2% of patients developed secondary malignancies following the ZEVALIN therapeutic regimen. One patient developed a Grade 1 meningioma, three developed acute myelogenous leukemia, and two developed a myelodysplastic syndrome. The onset of a second cancer was 8-34 months following the ZEVALIN therapeutic regimen and 4 to 14 years following the patients' diagnosis of NHL.

Immunogenicity: Of 211 patients who received the ZEVALIN therapeutic regimen in clinical trials and who were followed for 90 days, there were eight (3.8%) patients with evidence of human anti-mouse antibody (HAMA) (n=5) or human anti-chimeric antibody (HACA) (n=4) at any time during the course of the study. Two patients had low titers of HAMA prior to initiation of the ZEVALIN therapeutic regimen; one remained positive without an increase in titer while the other had a negative titer post-treatment. Three patients had evidence of HACA responses prior to initiation of the ZEVALIN therapeutic regimen; one had a marked increase in HACA titer while the other two had negative titers post-treatment. Of the three patients who had negative HAMA or HACA titers prior to the ZEVALIN therapeutic regimen, two developed HAMA in absence of HACA titers, and one had both HAMA and HACA positive titers post-treatment. Evidence of immunogenicity may be masked in patients who are lymphopenic. There has not been adequate evaluation of HAMA and HACA at delayed timepoints, concurrent with the recovery from lymphopenia at 6-12 months, to establish whether masking of the immunogenicity at early timepoints occurs. The data reflect the percentage of patients

whose test results were considered positive for antibodies to Ibritumomab or Rituximab using kinetic enzyme immunoassays to Ibritumomab and Rituximab. The observed incidence of antibody positivity in an assay is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors including sample handling and concomitant medications. Comparisons of the incidence of HAMA/HACA to the ZEVALIN therapeutic regimen with the incidence of antibodies to other products may be misleading.

OVERDOSAGE

Doses as high as 0.52 mCi/kg (19.2 MBq/kg) of Y-90 ZEVALIN were administered in ZEVALIN therapeutic regimen clinical trials and severe hematological toxicities were observed. No fatalities or second organ injury resulting from overdosage administrations were documented. However, single doses up to 50 mCi (1850 MBq) of Y-90 ZEVALIN, and multiple doses of 20 mCi (740 MBq) followed by 40 mCi (1480 MBq) of Y-90 ZEVALIN were studied in a limited number of subjects. In these trials, some patients required autologous stem cell support to manage hematological toxicity.

DOSAGE AND ADMINISTRATION

The ZEVALIN therapeutic regimen is administered in two steps: Step 1 includes a single infusion of 250 mg/m^2 Rituximab (not included in the ZEVALIN kits) preceding a fixed dose of 5.0 mCi (1.6 mg total antibody dose) of In-111 ZEVALIN administered as a 10 minute IV push. Step 2 follows step 1 by seven to nine days and consists of a second infusion of 250 mg/m^2 of Rituximab prior to 0.4 mCi/kg of Y-90 ZEVALIN administered as a 10 minute IV push.

Rituximab Administration: NOTE THAT THE DOSE OF RITUXIMAB IS LOWER WHEN USED AS PART OF THE ZEVALIN THERAPEUTIC REGIMEN, AS COMPARED TO THE DOSE OF RITUXIMAB WHEN USED AS A SINGLE AGENT. DO NOT ADMINISTER RITUXIMAB AS AN INTRAVENOUS PUSH OR BOLUS. Hypersensitivity reactions may occur (see WARNINGS). Premedication, consisting of acetaminophen and diphenhydramine, should be considered before each infusion of Rituximab.

ZEVALIN Therapeutic Regimen Dose Modification in Patients with Mild Thrombocytopenia: The Y-90 ZEVALIN dose should be reduced to 0.3 mCi/kg (11.1 MBq/kg) for patients with a baseline platelet count between 100,000 and 149,000 cells/mm^3.

Two separate and distinctly-labeled kits are ordered for the preparation of a single dose each of In-111 ZEVALIN and Y–90 ZEVALIN. In-111 ZEVALIN and Y-90 ZEVALIN are radiopharmaceuticals and should be used only by physicians and other professionals qualified by training and experienced in the safe use and handling of radionuclides. **Changing the ratio of any of the reactants in the radiolabeling process may adversely impact therapeutic results. In-111 ZEVALIN and Y-90 ZEVALIN should not be used in the absence of the Rituximab pre-dose.**

501 **Overview of Dosing Schedule:**

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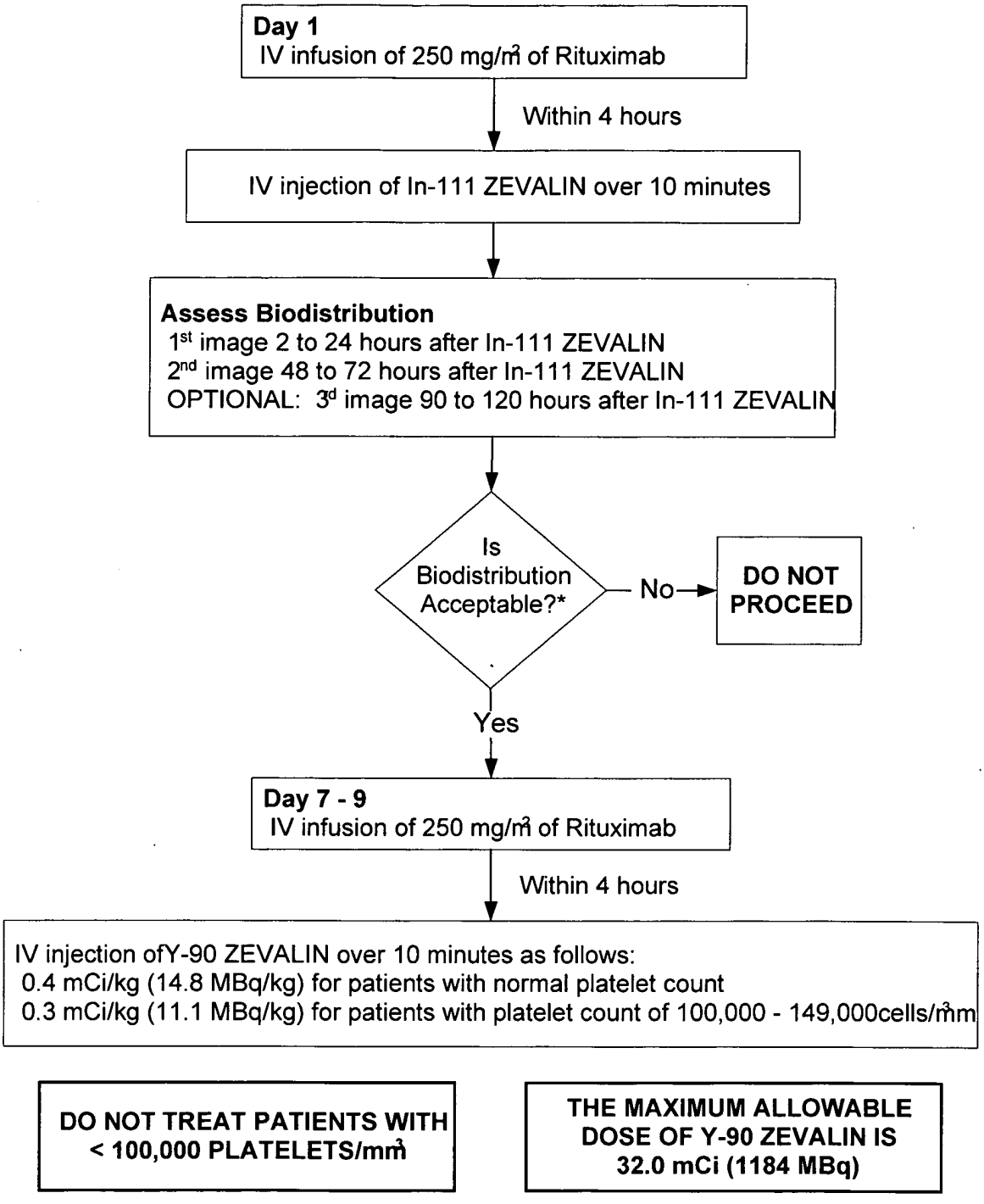

*See IMAGE ACQUISITION AND INTERPRETATION

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ZEVALIN Therapeutic Regimen Administration

Step 1:

First Rituximab Infusion: Rituximab at a dose of 250 mg/m^2 should be administered intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted with other drugs. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If hypersensitivity or an infusion-related event develops, the infusion should be temporarily slowed or interrupted (see WARNINGS). The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

In-111 ZEVALIN Injection: Within 4 hours following completion of the Rituximab dose, 5.0 mCi (1.6 mg total antibody dose) of In-111 ZEVALIN is injected intravenously (I.V.) over a period of 10 minutes.

Step 2:

Step 2 of the ZEVALIN therapeutic regimen is initiated seven to nine days following Step 1 administrations.

Second Rituximab Infusion: Rituximab at a dose of 250 mg/m^2 is administered I.V. at an initial rate of 100 mg/hr (50 mg/hr if infusion related events were documented during the first Rituximab administration) and increased by 100 mg/hr increments at 30 minute intervals, to a maximum of 400 mg/hr, as tolerated.

Y-90 ZEVALIN Injection:

Within 4 hours following completion of the Rituximab dose, Y-90 ZEVALIN at a dose of 0.4 mCi/kg (14.8 MBq/kg) actual body weight for patients with a platelet count >150,000 cells/mm^3, and 0.3 mCi/kg (11.1 MBq/kg) actual body weight for patients with a platelet count of 100,000-149,000 cells/mm^3 is injected intravenously (I.V.) over a period of 10 minutes. Precautions should be taken to avoid extravasation. A free flowing I.V. line should be established prior to Y-90 ZEVALIN injection. Close monitoring for evidence of extravasation during the injection of Y-90 ZEVALIN is required. If any signs or

symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. **The prescribed, measured, and administered dose of Y-90 ZEVALIN must not exceed the absolute maximum allowable dose of 32.0 mCi (1184 MBq), regardless of the patient's body weight. Do not give Y-90 ZEVALIN to patients with a platelet count <100,000/mm^3 (see WARNINGS).**

DIRECTIONS FOR PREPARATION OF RADIOLABELED ZEVALIN.

A. PREPARATION OF THE IN-111 ZEVALIN DOSE

GENERAL:

Read all directions thoroughly and assemble all materials before starting the radiolabeling procedure. Important, significant differences exist in the preparation of the In-111 ZEVALIN dose and the Y-90 ZEVALIN dose.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration. The dose calibrator must be operated in accordance with the manufacturer's specifications and quality control for the measurement of In-111.

Proper aseptic technique and precautions for handling radioactive materials should be employed. Waterproof gloves should be utilized in the preparation and during the determination of radiochemical purity of In-111 ZEVALIN. Appropriate shielding should be used during radiolabeling, and use of a syringe shield is recommended during administration to the patient. The radiolabeling of ZEVALIN shall be done according to the following directions.

Required materials not supplied in the kit:

A. Indium-111 Chloride Sterile Solution (In-111 Chloride) from Amersham Health, Inc. or Mallinckrodt, Inc.
B. Three sterile 1 mL syringes
C. One sterile 3 mL syringe
D. Two sterile 10 mL syringes with 18-20 G needles
E. Instant thin-layer chromatographic silica gel strips
F. 0.9% sodium chloride aqueous solution for the chromatography solvent
G. Developing chamber for chromatography
H. Suitable radioactivity counting apparatus
I. Filter, 0.22 micrometer, low-protein-binding
J. Vial and syringe shield

Method:

1. Sterile, pyrogen-free In-111 chloride must be used for the preparation of In-111 ZEVALIN. The use of high purity In-111 chloride manufactured by Amersham Health, Inc. or Mallinckrodt, Inc. is required.

2. Before radiolabeling, allow contents of the refrigerated carton to reach room temperature. Note: The ZEVALIN vial contains a protein solution that may develop translucent particulates. These particulates will be removed by filtration prior to administration.

3. Clean the rubber stoppers of all of the vials in the kit and the In-111 chloride vial with a suitable alcohol swab and allow to air dry.

4. Place the empty Reaction Vial in a suitable dispensing shield (pre-warmed to room temperature). To avoid the buildup of excessive pressure during the procedure, use a 10 mL syringe to withdraw 10 mL of air from the Reaction Vial.

5. Prior to initiating the radiolabeling reaction, determine the amount of each component needed according to the directions below:

    a. Calculate the volume of In-111 chloride that is equivalent to 5.5 mCi based on the activity concentration of the In-111 chloride stock.

    b. The volume of 50 mM sodium acetate solution needed is 1.2 times the volume of In-111 chloride solution determined in step 5.a., above. (The 50 mM sodium acetate is used to adjust the pH for the radiolabeling reaction.)

    c. Calculate the volume of Formulation Buffer needed to bring the Reaction Vial contents to a final volume of 10 mL. This is the volume of Formulation Buffer needed to protect the labeled product from radiolysis and to terminate the labeling reaction. For example, if volumes of 0.5 mL of In-111 chloride, 0.6 mL of sodium acetate and 1.0 mL of ZEVALIN were used, then the amount of formulation buffer would be 10-(0.5 + 0.6 + 1.0) = 7.9 mL.

6. With a sterile 1 mL syringe, transfer the calculated volume of 50 mM of sodium acetate to the empty Reaction Vial. Coat the entire inner surface of the Reaction Vial by gentle inversion or rolling.

7. Transfer 5.5 mCi of In-111 chloride to the Reaction Vial with a sterile 1 mL syringe. Mix the two solutions and coat the entire inner surface of the Reaction Vial by gentle inversion or rolling.

8. With a sterile 3 mL syringe, transfer 1.0 mL of ZEVALIN (Ibritumomab Tiuxetan) to the Reaction Vial. Coat the entire surface of the Reaction Vial by

gentle inversion or rolling. **Do not shake or agitate the vial contents, since this will cause foaming and denaturation of the protein.**

9. Allow the labeling reaction to proceed at room temperature for 30 minutes. Allowing the labeling reaction to proceed for a longer or shorter time may result in inadequate labeling.

10. **Immediately** after the 30-minute incubation period, using a sterile 10 mL syringe with a large bore needle (18 G - 20 G), transfer the calculated volume of Formulation Buffer from step 5.c. to the Reaction Vial. Gently add the Formulation Buffer down the side of the Reaction Vial. If necessary, to normalize air pressure, withdraw an equal volume of air. Coat the entire inner surface of the Reaction Vial by gentle inversion or rolling. Do not shake or agitate the vial contents. Avoid foaming.

11. Using the supplied labels, record the patient identification, the date and time of preparation, the total activity and volume, and the date and time of expiration, and affix these labels to the reaction vial and shielded reaction vial container.

12. Calculate the volume required for an In-111 ZEVALIN dose of 5 mCi. Withdraw the required volume from the Reaction Vial contents into a sterile 10 mL syringe with a large bore needle (18 G - 20 G). Assay the syringe and contents in a dose calibrator. The syringe should contain the dose of In-111 ZEVALIN to be administered to the patient. Using the supplied labels, record the patient identification, the date and time of preparation, the total activity and volume added, and the date and time of expiration, and affix these labels to the syringe and shielded unit dose container.

13. Determine Radiochemical purity. See Section C: Procedure for Determining Radiochemical Purity Section that follows DIRECTIONS FOR PREPARATION OF THE Y-90 ZEVALIN DOSE.

14. Indium-111 ZEVALIN should be stored at 2 - 8°C (36-46°F) until use and administered within 12 hours of radiolabeling.

15. See DOSAGE AND ADMINISTRATION: ZEVALIN Therapeutic Regimen Administration: Step 1

16. Discard vials, needles and syringes in accordance with local, state, and federal regulations governing radioactive and biohazardous waste.

B. PREPARATION OF THE Y-90 ZEVALIN DOSE

GENERAL:

Read all directions thoroughly and assemble all materials before starting the radiolabeling procedure. Important, significant differences exist in the preparation of the In-111 ZEVALIN dose and the Y-90 ZEVALIN dose.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration. The dose calibrator must be operated in accordance with the manufacturer's specifications and quality control for the measurement of Y-90.

Proper aseptic technique and precautions for handling radioactive materials should be employed. Waterproof gloves should be utilized in the preparation and during the determination of radiochemical purity of Y-90 ZEVALIN. Appropriate shielding should be used during radiolabeling, and use of a syringe shield is recommended during administration to the patient. The radiolabeling of ZEVALIN shall be done according to the following directions.

Required materials not supplied in the kit:

A. Yttrium-90 Chloride Sterile Solution from MDS Nordion (shipped directly from MDS Nordion upon placement of an order for the Y-90 ZEVALIN kit)
B. Three sterile 1 mL syringes
C. One sterile 3 mL syringe
D. Two sterile 10 mL syringes with 18-20 G needles
E. Instant thin-layer chromatographic silica gel strips (ITLC-SG)
F. 0.9% sodium chloride aqueous solution for the chromatography solvent
G. Suitable radioactivity counting apparatus
H. Developing chamber for chromatography
I. Filter, 0.22 micrometer, low-protein-binding
J. Vial and syringe shield

Method:

1. Sterile, pyrogen-free Y-90 chloride must be used for the preparation of Y-90 ZEVALIN. The use of high purity Y-90 chloride manufactured by MDS Nordion is required.

2. Before radiolabeling, allow the contents of the refrigerated carton to reach room temperature. Note: The ZEVALIN vial contains a protein solution that may develop translucent particulates. These particulates will be removed by filtration prior to administration.

3. Clean the rubber stoppers of all of the vials in the kit and the Y-90 chloride vial with a suitable alcohol swab and allow to air dry.

4. Place the empty Reaction Vial in a suitable dispensing shield (pre-warmed to room temperature). To avoid the buildup of excessive pressure during the procedure, use a 10 mL syringe to withdraw 10 mL of air from the Reaction Vial.

5. Prior to initiating the radiolabeling reaction, determine the amount of each component needed according to the directions below:

    a. Calculate the volume of Y-90 chloride that is equivalent to 40 mCi based on the activity concentration of the Y-90 chloride stock.

    b. The volume of 50 mM sodium acetate solution needed is 1.2 times the volume of Y-90 chloride solution determined in step 5.a., above. (The 50 mM sodium acetate is used to adjust the pH for the radiolabeling reaction.)

    c. Calculate the volume of Formulation Buffer needed to bring the Reaction Vial contents to a final volume of 10 mL. This is the volume of Formulation Buffer needed to protect the labeled product from radiolysis and to terminate the labeling reaction. For example if the volumes were 0.5 mL of Y-90 chloride, 0.6 mL of sodium acetate and 1.3 mL of ZEVALIN, then the amount of formulation buffer would be 10-(0.5 + 0.6 + 1.3) = 7.6 mL.

6. With a sterile 1 mL syringe, transfer the calculated volume of 50 mM sodium acetate to the empty Reaction Vial. Coat the entire inner surface of the Reaction Vial by gentle inversion or rolling.

7. Transfer 40 mCi of Y-90 chloride to the Reaction Vial with a sterile 1 mL syringe. Mix the two solutions and coat the entire inner surface of the Reaction Vial by gentle inversion or rolling.

8. With a sterile 3 mL syringe, transfer 1.3 mL of ZEVALIN (Ibritumomab Tiuxetan) to the Reaction Vial. Coat the entire surface of the Reaction Vial by

gentle inversion or rolling. **Do not shake or agitate the vial contents, since this will cause foaming and denaturation of the protein.**

9. Allow the labeling reaction to proceed at room temperature for 5 minutes. Allowing the labeling reaction to proceed for a longer or shorter time may result in inadequate labeling.

10. **Immediately** after the 5-minute incubation period, using a sterile 10 mL syringe with a large bore needle (18 G - 20 G), transfer the calculated volume of Formulation Buffer from step 5.c. to the Reaction Vial, terminating incubation. Gently add the Formulation Buffer down the side of the Reaction Vial. If necessary to normalize air pressure, withdraw an equal volume of air. Coat the entire inner surface of the Reaction Vial by gentle inversion or rolling. Do not shake or agitate the vial contents. Avoid foaming.

11. Using the supplied labels, record the patient identification, the date and time of preparation, the total activity and volume, and the date and time of expiration and affix these labels to the reaction vial and shielded reaction vial container.

12. Calculate the volume required for a Y-90 ZEVALIN dose of 0.4 mCi/kg (14.8 MBq/kg) actual body weight for patients with normal platelet count, and 0.3 mCi/kg (11.1 MBq/kg) actual body weight for patients with platelet count of 100,000 - 149,000 cells/mm^3. **The prescribed, measured, and administered dose of Y-90 ZEVALIN must not exceed the absolute maximum allowable dose of 32.0 mCi (1184 MBq), regardless of the patient's body weight.** Withdraw the required volume from the Reaction Vial contents into a sterile 10 mL syringe with a large bore needle (18 G - 20 G). Assay the syringe and contents in a dose calibrator. The dose calibrator must be operated in accordance with the manufacturer's specifications and quality control for the measurement of Y-90. The syringe should contain the dose of Y-90 ZEVALIN to be administered to the patient, and should be within 10% of the actual prescribed dose of Y-90

ZEVALIN, not to exceed a maximum dose of 32.0 mCi. Do not exceed ± 10% of the prescribed dose. Using the supplied labels, record the patient identification, the date and time of preparation, the total activity and volume added, and the date and time of expiration and affix these labels to the syringe and shielded unit dose container.

13. Determine Radiochemical Purity. See Section C: Procedure for Determining Radiochemical Purity Section that follows these DIRECTIONS FOR PREPARATION OF THE Y-90 ZEVALIN DOSE.

14. Yttrium-90 ZEVALIN should be stored at 2 - 8°C (36-46°F) until use and administered within 8 hours of radiolabeling.

15. See DOSAGE AND ADMINISTRATION: ZEVALIN Therapeutic Regimen Administration: Step 2.

16. Discard vials, needles and syringes in accordance with local, state, and federal regulations governing radioactive and biohazardous waste.

Yttrium-90 ZEVALIN is suitable for administration on an outpatient basis. Beyond the use of vial and syringe shields for preparation and injection, no special shielding is necessary.

C. PROCEDURE FOR DETERMINING RADIOCHEMICAL PURITY (RCP)

The following procedure should be used for both In-111 ZEVALIN and Y-90 ZEVALIN:

A. At room temperature, place a small drop of either In-111 ZEVALIN or Y-90 ZEVALIN at the origin of an ITLC-SG strip.

B. Place the ITLC-SG strip into a chromatography chamber with the origin at the bottom and the solvent front at the top. Allow the solvent (0.9% NaCl) to

migrate at least 5 cm from the bottom of the strip. Remove the strip from the chamber and cut the strip in half. Count each half of the ITLC-SG strip for one minute (CPM) with a suitable counting apparatus.

C. Calculate the percent RCP as follows:

$$\% \text{ RCP} = \frac{\text{CPM bottom half}}{\text{CPM bottom half} + \text{CPM top half}} \text{ X } 100$$

D. If the radiochemical purity is <95%, the ITLC procedure should be repeated. If repeat testing confirms that radiochemical purity is <95%, the preparation should not be administered.

IMAGE ACQUISITION AND INTERPRETATION

The biodistribution of In-111 ZEVALIN should be assessed by a visual evaluation of whole body planar view anterior and posterior gamma images at 2 - 24 hours and 48 – 72 hours after injection. To resolve ambiguities, a third image at 90 – 120 hours may be necessary. Images should be acquired using a large field of view gamma camera equipped with a medium energy collimator. The gamma camera should be calibrated using the 171 and 245 keV photopeaks for In-111 with a 15% – 20% symmetric window. Using a 256 x 1024 computer acquisition matrix, the scan speed should be 10 cm/min for the first scan, 7 cm/min for the second scan, and 5 cm/min for the optional third scan.

The radiopharmaceutical is expected to be easily detectable in the blood pool areas at the first time point, with less activity in the blood pool on later images. Moderately high to high uptake is seen in the normal liver and spleen, with low uptake in the lungs, kidneys, and urinary bladder. Localization to lymphoid aggregates in the bowel wall has been reported. Tumor uptake may be visualized in soft tissue as areas of increased intensity, and tumor-bearing areas in normal organs may be seen as areas of increased or decreased intensity.

If a visual inspection of the gamma images reveals an altered biodistribution, the patient should not proceed to the Y-90 ZEVALIN dose. The patient may be considered to have an altered biodistribution if the blood pool is not visualized on the first image indicating

rapid clearance of the radiopharmaceutical by the reticuloendothelial system to the liver, spleen, and/or marrow. Other potential examples of altered biodistribution may include diffuse uptake in the normal lungs or kidneys more intense than the liver on the second or third image.

During ZEVALIN clinical development, individual tumor radiation absorbed dose estimates as high as 778 cGy/mCi have been reported. Although solid organ toxicity has not been directly attributed to radiation from adjacent tumors, careful consideration should be applied before proceeding with treatment in patients with very high tumor uptake next to critical organs or structures.

HOW SUPPLIED

The In-111 ZEVALIN kit provides for the radiolabeling of Ibritumomab Tiuxetan with In-111. The Y-90 ZEVALIN kit provides for the radiolabeling of Ibritumomab Tiuxetan with Y-90.

The kit for the preparation of a single dose of In-111 ZEVALIN includes four vials: one ZEVALIN vial containing 3.2 mg of Ibritumomab Tiuxetan in 2 mL of 0.9% sodium chloride solution; one 50 mM Sodium Acetate vial; one Formulation Buffer vial; one empty Reaction vial and four identification labels.

The kit for the preparation of a single dose of Y-90 ZEVALIN includes four vials: one ZEVALIN vial containing 3.2 mg of Ibritumomab Tiuxetan in 2 mL of 0.9% sodium chloride solution; one 50 mM Sodium Acetate vial; one Formulation Buffer vial; one empty Reaction vial and four identification labels.

The contents of all vials are sterile, pyrogen-free and contain no preservatives.

The Indium-111 Chloride Sterile Solution (In-111 Chloride) must be ordered separately from either Amersham Health, Inc. or Mallinckrodt, Inc. at the time the In-111

ZEVALIN kit is ordered. The Yttrium-90 Chloride Sterile Solution will be shipped directly from MDS Nordion upon placement of an order for the Y-90 ZEVALIN kit.

Storage

Store at 2 -8°C (36-46°F). Do not freeze.

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Rx Only

In-111 ZEVALIN kit, NDC 64406-104-04

Y-90 ZEVALIN kit, NDC 64406-103-03

3030 Callan Road

San Diego, CA 92121

U.S. License Number 1235

Issue date: January 2002

Exhibit B

U.S. Patent 5,776,456

US005776456A

United States Patent [19]

Anderson et al.

[11] Patent Number: 5,776,456

[45] Date of Patent: Jul. 7, 1998

[54] **THERAPEUTIC APPLICATION OF CHIMERIC AND RADIOLABELED ANTIBODIES TO HUMAN B LYMPHOCYTE RESTRICTED DIFFERENTIATION ANTIGEN FOR TREATMENT OF B CELL LYMPHOMA**

[75] Inventors: **Darrell R. Anderson**, Escondido; **Nabil Hanna**, Olivenhain; **John E. Leonard**, Encinitas; **Roland A. Newman**; **Mitchell E. Reff**, both of San Diego; **William H. Rastetter**, Rancho Sante Fe, all of Calif.

[73] Assignee: **IDEC Pharmaceuticals Corporation**, San Diego, Calif.

[21] Appl. No.: **476,275**

[22] Filed: **Jun. 7, 1995**

Related U.S. Application Data

[60] Division of Ser. No. 149,099, Nov. 3, 1993, which is a continuation-in-part of Ser. No. 978,891, Nov. 13, 1992, abandoned.

[51] **Int. Cl.**[6] **A61K 39/395**; A61K 51/00; C07K 16/28; C07K 16/30

[52] **U.S. Cl.** **424/133.1**; 424/1.49; 424/143.1; 424/144.1; 424/153.1; 424/155.1; 424/173.1; 424/174.1; 424/800; 424/801; 435/320.1; 435/344; 435/344.1; 435/328; 530/387.3; 530/388.22; 530/388.73; 530/388.8; 530/389.7; 530/391.3; 530/809; 530/867; 935/89; 935/104; 935/107

[58] **Field of Search** 424/133.1, 143.1, 424/144.1, 153.1, 155.1, 173.1, 174.1, 1.49, 800, 801; 435/69.6, 70.21, 172.2, 209, 240.27, 320.1, 89, 104, 107, 344, 344.1, 328, 346; 530/387.3, 388.22, 388.73, 388.8, 389.7, 391.3, 809, 867; 536/23.53

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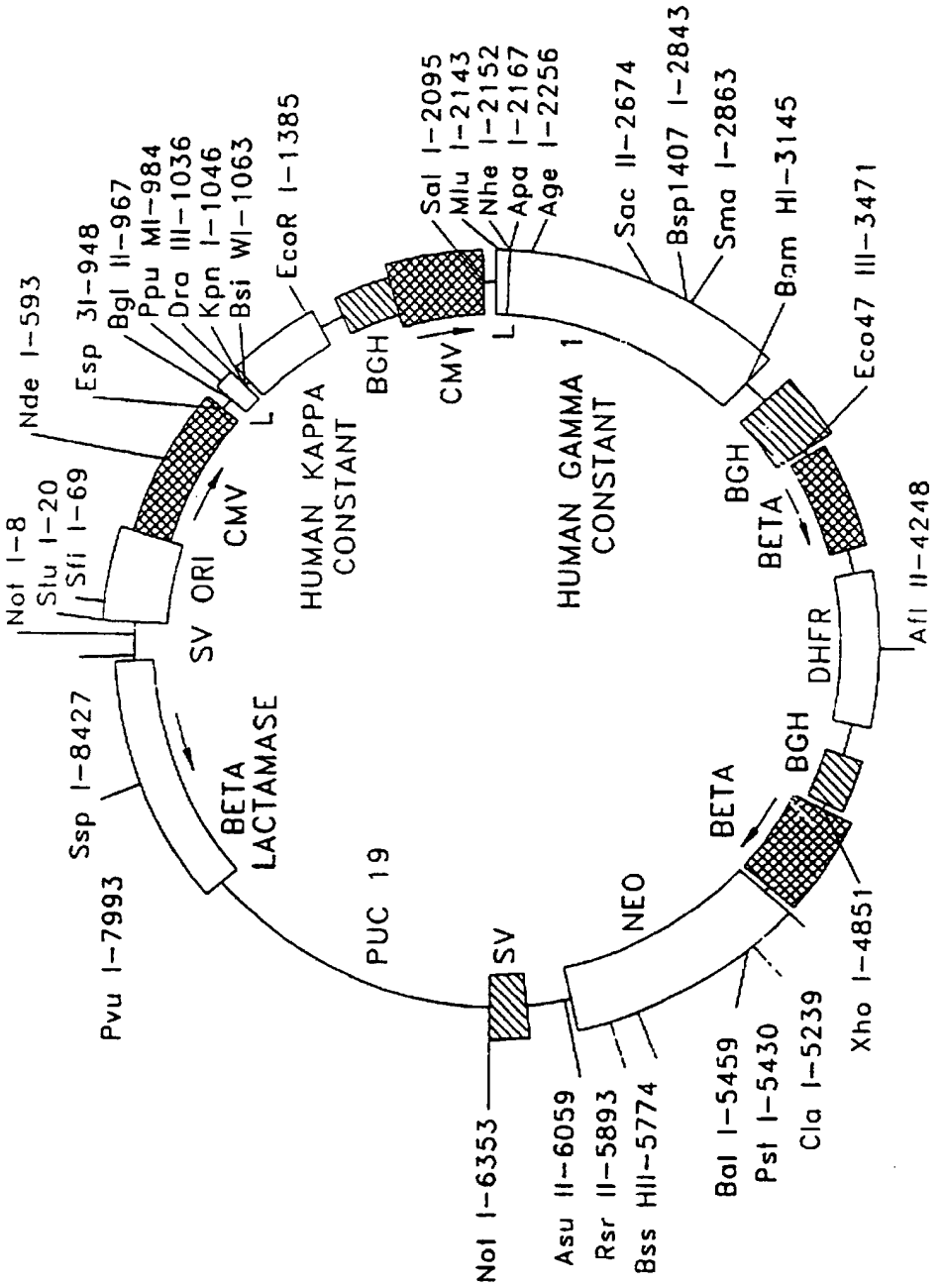
Primary Examiner—Ronald B. Schwadron
Attorney, Agent, or Firm—Burns, Doane, Swecker & Mathis, LLP

[57] **ABSTRACT**

Disclosed herein are therapeutic treatment protocols designed for the treatment of B cell lymphoma. These protocols are based upon therapeutic strategies which include the use of administration of immunologically active mouse/human chimeric anti-CD20 antibodies, radiolabeled anti-CD20 antibodies, and cooperative strategies comprising the use of chimeric anti-CD20 antibodies and radiolabeled anti-CD20 antibodies.

14 Claims, 21 Drawing Sheets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Bsi WI-1063
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Mlu I-2143
Nhe I-2152
Apa I-2167
Age I-2256
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Bsp1407 I-2843
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Afl II-4248
Xho I-4851
Cla I-5239
Pst I-5430
Bal I-5459
Bss HII-5774
Rsr II-5893
Asu II-6059
Not I-6353
Pvu I-7993
Ssp I-8427
SV ORI
CMV
L
HUMAN KAPPA CONSTANT
BGH
CMV
L
HUMAN GAMMA 1 CONSTANT
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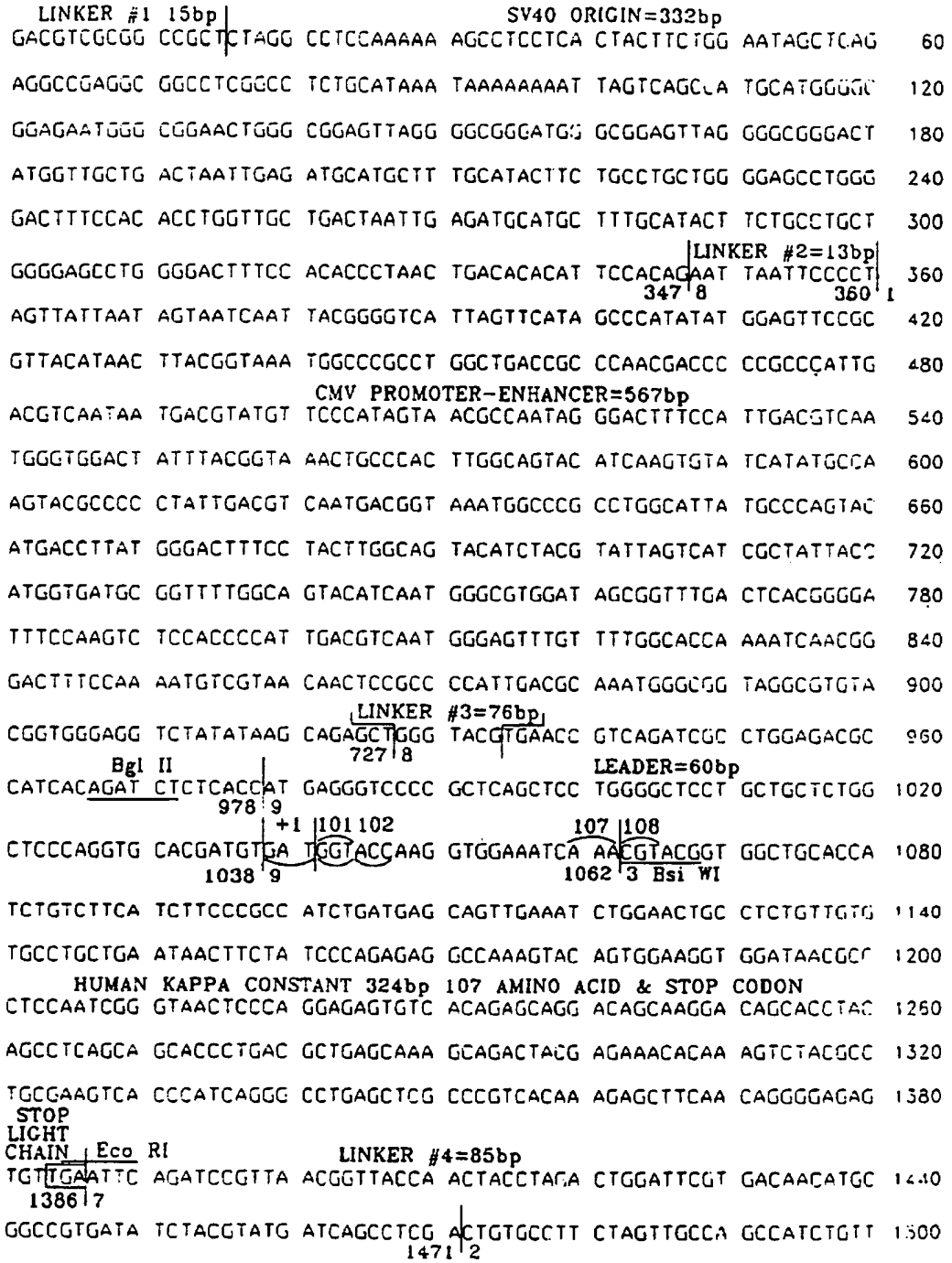
BETA
DHFR
BGH
BETA
NEO
SV
PUC 19
BETA LACTAMASE

FIG. 1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SV40 ORIGIN=332bp
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CMV PROMOTER-ENHANCER=567bp
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LEADER=60bp
Bgl II
HUMAN KAPPA CONSTANT 324bp 107 AMINO ACID & STOP CODON
STOP
LIGHT
CHAIN
Eco RI
Bsi WI
LINKER #4=85bp

FIG. 2A

```
GTTTGCCCCT CCCCCGTGCC TTCCTTGACC CTGGAAGGTG CCACTCCCAC TGTCCTTTCC 1560
                                BGH poly A=231bp
TAATAAAATG AGGAAATTGC ATCGCATTGT CTGAGTAGGT GTCATTCTAT TCTGGGGGGT 1620
GGGGTGGGGC AGGACAGCAA GGGGGAGGAT TGGGAAGACA ATAGCAGGCA TGCTGGGGAT 1680
                          | LINKER #5=15bp |
GCGGTGGGCT CTATGGAACC AGCTGGGGCT CGACAGCTAT GCCAAGTACG CCCCCTATTG 1740
                     1702 3          1717 8
ACGTCAATGA CGGTAAATGG CCCGCCTGGC ATTATGCCCA GTACATGACC TTATGGGACT 1800
TTCCTACTTG GCAGTACATC TACGTATTAG TCATCGCTAT TACCATGGTG ATGCGGTTTT 1860
                        CMV PROMOTER-ENHANCER=334bp
GGCAGTACAT CAATGGGCGT GGATAGCGGT TTGACTCACG GGGATTTCCA AGTCTCCACC 1920
CCATTGACGT CAATGGGAGT TTGTTTTGGC ACCAAAATCA ACGGGACTTT CCAAAATGTC 1980
GTAACAACTC CGCCCCATTG ACGCAAATGG GCGGTAGGCG TGTACGGTGG GAGGTCTATA 2040
        |LINKER #6=7bp|                                        Sal I
TAAGCAGAGC TGGGTACGTC CTCACATTCA GTGATCAGCA CTGAACACAG ACCCGTCGAC 2100
        2051 2 2058 9
                                LEADER=51bp        Mlu I 2151 |2 Nhe I
ATGGGTTGGA GCCTCATCTT GCTCTTCCTT GTCGCTGTTG CTACGCGTGT CGCTAGCACC 2160
 START HEAVY CHAIN                                  -5 -4 -3 114 115
AAGGGCCCAT CGGTCTTCCC CCTGGCACCC TCCTCCAAGA GCACCTCTGG GGGCACAGCG 2220
GCCCTGGGCT GCCTGGTCAA GGACTACTTC CCCGAACCGG TGACGGTGTC GTGGAACTCA 2280
GGCGCCCTGA CCAGCGGCGT GCACACCTTC CCGGCTGTCC TACAGTCCTC AGGACTCTAC 2340
                        HUMAN GAMMA 1 CONSTANT
TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAGCTTGG GCACCCAGAC CTACATCTGC 2400
                    993bp=330 AMINO ACID & STOP CODON
AACGTGAATC ACAAGCCCAG CAACACCAAG GTGGACAAGA AAGCAGAGCC CAAATCTTGT 2460
GACAAAACTC ACACATGCCC ACCGTGCCCA GCACCTGAAC TCCTGGGGGG ACCGTCAGTC 2520
TTCCTCTTCC CCCCAAAACC CAAGGACACC CTCATGATCT CCCGGACCCC TGAGGTCACA 2580
TGCGTGGTGG TGGACGTGAG CCACGAAGAC CCTGAGGTCA AGTTCAACTG GTACGTGGAC 2640
GGCGTGGAGG TGCATAATGC CAAGACAAAG CCGCGGGAGG AGCAGTACAA CAGCACGTAC 2700
CGTGTGGTCA GCGTCCTCAC CGTCCTGCAC CAGGACTGGC TGAATGGCAA GGAGTACAAG 2760
TGCAAGGTCT CCAACAAAGC CCTCCCAGCC CCCATCGAGA AAACCATCTC CAAAGCCAAA 2820
GGGCAGCCCC GAGAACCACA GGTGTACACC CTGCCCCCAT CCCGGGATGA GCTGACCAGG 2880
AACCAGGTCA GCCTGACCTG CCTGGTCAAA GGCTTCTATC CCAGCGACAT CGCCGTGGAG 2940
TGGGAGAGCA ATGGGCAGCC GGAGAACAAC TACAAGACCA CGCCTCCCGT GCTGGACTCC 3000
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FIG. 2B

```
GATGGCTCCT TCTTCCTCTA CAGCAAGCTC ACCGTGGACA AGAGCAGGTG GCAGCAGGGG 3060

AACGTCTTCT CATGCTCCGT GATGCATGAG GCTCTGCACA ACCACTACAC GCAGAAGAGC 3120

                STOP HEAVY CHAIN | Bam HI          LINKER #7=81bp
CTCTCCCTGT CTCCGGGTAA ATGAGGATCC GTTAACGGTT ACCAACTACC TAGACTGGAT 3180
                      3144 | 5

TCGTGACAAC ATGCGGCCGT GATATCTACG TATGATCAGC CTCGACTGTG CCTTCTAGTT 3240
                                              3225 | 6

GCCAGCCATC TGTTGTTTGC CCCTCCCCCG TGCCTTCCTT GACCCTGGAA GGTGCCACTC 3300

        BOVINE GROWTH HORMONE POLYADENYLATION REGION=231bp
CCACTGTCCT TTCCTAATAA AATGAGGAAA TTGCATCGCA TTGTCTGAGT AGGTGTCATT 3360

CTATTCTGGG GGGTGGGGTG GGGCAGGACA GCAAGGGGGA GGATTGGGAA GACAATAGCA 3420

                                          LINKER #8=34bp
GGCATGCTGG GGATGCGGTG GGCTCTATGG AACCAGCTGG GGCTCGACAG CGCTGGATCT 3480
                                    3456 | 7

CCCGATCCCC| AGCTTTGCTT CTCAATTTCT TATTTGCATA ATGAGAAAAA AAGGAAAATT 3540
    3490 | 1

AATTTTAACA CCAATTCAGT AGTTGATTGA GCAAATGCGT TGCCAAAAAG GATGCTTTAG 3600

                MOUSE BETA GLOBIN MAJOR PROMOTER=366bp
AGACAGTGTT CTCTGCACAG ATAAGGACAA ACATTATTCA GAGGGAGTAC CCAGAGCTGA 3660

GACTCCTAAG CCAGTGAGTG GCACAGCATT CTAGGGAGAA ATATGCTTGT CATCACCGAA 3720

GCCTGATTCC GTAGAGCCAC ACCTTGGTAA GGGCCAATCT GCTCACACAG GATAGAGAGG 3780

GCAGGAGCCA GGGCAGAGCA TATAAGGTGA GGTAGGATCA GTTGCTCCTC ACATTTGCTT 3840

          | LINKER #9=19bp          | 5' UNTRANSLATED DHFR=82bp
CTGACATAGT TGTGTTGGGA GCTTGGATAG CTTGGACAGC TCAGGGCTGC GATTTCGCGC 3900
            3856 | 7                 3875 | 6

                                                  START DHFR
CAAACTTGAC GGCAATCCTA GCGTGAAGGC TGGTAGGATT TTATCCCCGC TGCCATGATG 3960
                                                        3957 | 8

GTTCGACCAT TGAACTGCAT CGTCGCCGTG TCCCAAAATA TGGGGATTGG CAAGAACGGA 4020

GACCTACCCT GGCCTCCGCT CAGGAACGAG TTCAAGTACT TCCAAAGAAT GACCACAACC 4080

TCTTCAGTGG AAGGTAAACA GAATCTGGTG ATTATGGGTA GGAAAACCTG GTTCTCCATT 4140

        MOUSE DHFR=564bp=187 AMINO ACID & STOP CODON
CCTGAGAAGA ATCGACCTTT AAAGGACAGA ATTAATATAG TTCTCAGTAG AGAACTCAAA 4200

GAACCACCAC GAGGAGCTCA TTTTCTTGCC AAAAGTTTGG ATGATGCCTT AAGACTTATT 4260

GAACAACCGG AATTGGCAAG TAAAGTAGAC ATGGTTTGGA TAGTCGGAGG CAGTTCTGTT 4320

TACCAGGAAG CCATGAATCA ACCAGGCCAC CTTAGACTCT TTGTGACAAG GATCATGCAG 4380

GAATTTGAAA GTGACACGTT TTTCCCAGAA ATTGATTTGG GGAAATATAA ACTTCTCCCA 4440

GAATACCCAG GCGTCCTCTC TGAGGTCCAG GAGGAAAAAG GCATCAAGTA TAAGTTTGAA 4500
```

FIG. 2C

STOP DHFR
GTCTACGAGA AGAAAGACTA ACAGGAAGAT GCTTTCAAGT TCTCTGCTCC CCTCCTAAAG 4560
4521 2

3' UNTRANSLATED DHFR=82bp LINKER #10=10bp
TCATGCATTT TTATAAGACC ATGGGACTTT TGCTGGCTTT AGATCAGCCT CGACTGTGCC 4620
4603 4 4613 4

TTCTAGTTGC CAGCCATCTG TTGTTTGCCC CTCCCCCGTG CCTTCCTTGA CCCTGGAAGG 4680

BOVINE GROWTH HORMONE POLYADENYLATION REGION=231bp
TGCCACTCCC ACTGTCCTTT CCTAATAAAA TGAGGAAATT GCATCGCATT GTCTGAGTAG 4740

GTGTCATTCT ATTCTGGGGG GTGGGGTGGG GCAGGACAGC AAGGGGGAGG ATTGGGAAGA 4800

LINKER #11=17bp
CAATAGCAGG CATGCTGGGG ATGCGGTGGG CTCTATGGAA CCAGCTGGGG CTCGAGCTAC 4860
4844 5

TAGCTTTGCT TCTCAATTTC TTATTTGCAT AATGAGAAAA AAAGGAAAAT TAATTTTAAC 4920

ACCAATTCAG TAGTTGATTG AGCAAATGCG TTGCCAAAAA GGATGCTTTA GAGACAGTGT 4980

MOUSE BETA GLOBIN MAJOR PROMOTER=366bp
TCTCTGCACA GATAAGGACA AACATTATTC AGAGGGAGTA CCCAGAGCTG AGACTCCTAA 5040

GCCAGTGAGT GGCACAGCAT TCTAGGGAGA AATATGCTTG TCATCACCGA AGCCTGATTC 5100

CGTAGAGCCA CACCTTGGTA AGGGCCAATC TGCTCACACA GGATAGAGAG GGCAGGAGCC 5160

AGGGCAGAGC ATATAAGGTG AGGTAGGATC AGTTGCTCCT CACATTTGCT TCTGACATAG 5220

LINKER #12=21bp START NEO
TTGTGTTGGG AGCTTGGATC GATCCTCTAT GGTTGAACAA GATGGATTGC ACGCAGGTTC 5280
5227 8 5248 9

TCCGGCCGCT TGGGTGGAGA GGCTATTCGG CTATGACTGG GCACAACAGA CAATCGGCTG 5340

CTCTGATGCC GCCGTGTTCC GGCTGTCAGC GCAGGGGCGC CCGGTTCTTT TTGTCAAGAC 5400

NEOMYCIN PHOSPHOTRANSFERASE
CGACCTGTCC GGTGCCCTGA ATGAACTGCA GGACGAGGCA GCGCGGCTAT CGTGGCTGGC 5460

795bp=264 AMINO ACIDS & STOP CODON
CACGACGGGC GTTCCTTGCG CAGCTGTGCT CGACGTTGTC ACTGAAGCGG GAAGGGACTG 5520

GCTGCTATTG GGCGAAGTGC CGGGGCAGGA TCTCCTGTCA TCTCACCTTG CTCCTGCCGA 5580

GAAAGTATCC ATCATGGCTG ATGCAATGCG GCGGCTGCAT ACGCTTGATC CGGCTACCTG 5640

CCCATTCGAC CACCAAGCGA AACATCGCAT CGAGCGAGCA CGTACTCGGA TGGAAGCCGG 5700

TCTTGTCGAT CAGGATGATC TGGACGAAGA GCATCAGGGG CTCGCGCCAG CCGAACTGTT 5760

CGCCAGGCTC AAGGCGCGCA TGCCCGACGG CGAGGATCTC GTCGTGACCC ATGGCGATGC 5820

CTGCTTGCCG AATATCATGG TGGAAAATGG CCGCTTTTCT GGATTCATCG ACTGTGGCCG 5880

GCTGGGTGTG GCGGACCGCT ATCAGGACAT AGCGTTGGCT ACCCGTGATA TTGCTGAAGA 5940

GCTTGGCGGC GAATGGGCTG ACCGCTTCCT CGTGCTTTAC GGTATCGCCG CTTCCCGATTC 6000

FIG. 2D

STOP NEO
GCAGCGCATC GCCTTCTATC GCCTTCTTGA CGAGTTCTTC TGAGCGGGAC TCTGGGGTTC 6060
6043 4

GAAATGACCG ACCAAGCGAC GCCCAACCTG CCATCACGAG ATTTCGATTC CACCGCCGCC 6120

3' UNTRANSLATED NEO=173bp
TTCTATGAAA GGTTGGGCTT CGGAATCGTT TTCCGGGACG CCGGCTGGAT GATCCTCCAG 6180

CGCGGGGATC TCATGCTGGA GTTCTTCGCC CACCCCAACT TGTTTATTGC AGCTTATAAT 6240
6216 7

GGTTACAAAT AAAGCAATAG CATCACAAAT TTCACAAATA AAGCATTTTT TTCACTGCAT 6300

SV40 POLY A EARLY=133bp LINKER #13=19bp
TCTAGTTGTG GTTTGTCCAA ACTCATCAAT CTATCTTATC ATGTCTGGAT CGCGGCCGCG 6360
6349 50

ATCCCGTCGA GAGCTTGGCG TAATCATGGT CATAGCTGTT TCCTGTGTGA AATTGTTATC 6420
6368 9

CGCTCACAAT TCCACACAAC ATACGAGCCG GAAGCATAAA GTGTAAAGCC TGGGGTGCCT 6480

AATGAGTGAG CTAACTCACA TTAATTGCGT TGCGCTCACT GCCCGCTTTC CAGTCGGGAA 6540

ACCTGTCGTG CCAGCTGCAT TAATGAATCG GCCAACGCGC GGGGAGAGGC GGTTTGCGTA 6600

PVC 19
TTGGGCGCTC TTCCGCTTCC TCGCTCACTG ACTCGCTGCG CTCGGTCGTT CGGCTGCGGC 6660

GAGCGGTATC AGCTCACTCA AAGGCGGTAA TACGGTTATC CACAGAATCA GGGGATAACG 6720

CAGGAAAGAA CATGTGAGCA AAAGGCCAGC AAAAGGCCAG GAACCGTAAA AAGGCCGCGT 6780

6792=BACTERIAL ORIGIN OF REPLICATION
TGCTGGCGTT TTTCCATAGG CTCCGCCCCC CTGACGAGCA TCACAAAAAT CGACGCTCAA 6840

GTCAGAGGTG GCGAAACCCG ACAGGACTAT AAAGATACCA GGCGTTTCCC CCTGGAAGCT 6900

CCCTCGTGCG CTCTCCTGTT CCGACCCTGC CGCTTACCGG ATACCTGTCC GCCTTTCTCC 6960

CTTCGGGAAG CGTGGCGCTT TCTCAATGCT CACGCTGTAG GTATCTCAGT TCGGTGTAGG 7020

TCGTTCGCTC CAAGCTGGGC TGTGTGCACG AACCCCCCGT TCAGCCCGAC CGCTGCGCCT 7080

TATCCGGTAA CTATCGTCTT GAGTCCAACC CGGTAAGACA CGACTTATCG CCACTGGCAG 7140

CAGCCACTGG TAACAGGATT AGCAGAGCGA GGTATGTAGG CGGTGCTACA GAGTTCTTGA 7200

AGTGGTGGCC TAACTACGGC TACACTAGAA GGACAGTATT TGGTATCTGC GCTCTGCTGA 7260

AGCCAGTTAC CTTCGGAAAA AGAGTTGGTA GCTCTTGATC CGGCAAACAA ACCACCGCTG 7320

GTAGCGGTGG TTTTTTTGTT TGCAAGCAGC AGATTACGCG CAGAAAAAAA GGATCTCAAG 7380

AAGATCCTTT GATCTTTTCT ACGGGGTCTG ACGCTCAGTG GAACGAAAAC TCACGTTAAG 7440

GGATTTTGGT CATGAGATTA TCAAAAAGGA TCTTCACCTA GATCCTTTTA AATTAAAAAT 7500

FIG. 2E

STOP BETA LACTAMASE

```
GAAGTTTTAA ATCAATCTAA AGTATATATG AGTAAACTTG GTCTGACAGT TACCAATGCT 7560
                                                  7550
TAATCAGTGA GGCACCTATC TCAGCGATCT GTCTATTTCG TTCATCCATA GTTGCCTGAC 7620
TCCCCGTCGT GTAGATAACT ACGATACGGG AGGGCTTACC ATCTGGCCCC AGTGCTGCAA 7680
TGATACCGCG AGACCCACGC TCACCGGCTC CAGATTTATC AGCAATAAAC CAGCCAGCCG 7740
                BETA LACTAMASE=861bp
GAAGGGCCGA GCGCAGAAGT GGTCCTGCAA CTTTATCCGC CTCCATCCAG TCTATTAATT 7800
                286 AMINO ACID & STOP CODON
GTTGCCGGGA AGCTAGAGTA AGTAGTTCGC CAGTTAATAG TTTGCGCAAC GTTGTTGCCA 7860
TTGCTACAGG CATCGTGGTG TCACGCTCGT CGTTTGGTAT GGCTTCATTC AGCTCCGGTT 7920
CCCAACGATC AAGGCGAGTT ACATGATCCC CCATGTTGTG CAAAAAAGCG GTTAGCTCCT 7980
TCGGTCCTCC GATCGTTGTC AGAAGTAAGT TGGCCGCAGT GTTATCACTC ATGGTTATGG 8040
CAGCACTGCA TAATTCTCTT ACTGTCATGC CATCCGTAAG ATGCTTTTCT GTGACTGGTG 8100
AGTACTCAAC CAAGTCATTC TGAGAATAGT GTATGCGGCG ACCGAGTTGC TCTTGCCCGG 8160
CGTCAATACG GGATAATACC GCGCCACATA GCAGAACTTT AAAAGTGCTC ATCATTGGAA 8220
AACGTTCTTC GGGGCGAAAA CTCTCAAGGA TCTTACCGCT GTTGAGATCC AGTTCGATGT 8280
AACCCACTCG TGCACCCAAC TGATCTTCAG CATCTTTTAC TTTCACCAGC GTTTCTGGGT 8340
GAGCAAAAAC AGGAAGGCAA AATGCCGCAA AAAAGGGAAT AAGGGCGACA CGGAAATGTT 8400
        START BETA LACTAMASE
GAATACTCAT ACTCTTCCTT TTTCAATATT ATTGAAGCAT TTATCAGGGT TATTGTCTCA 8460
        8410
TGAGCGGATA CATATTTGAA TGTATTTAGA AAAATAAACA AATAGGGGTT CCGCGCACAT 8520
TTCCCCGAAA AGTGCCACCT
```

FIG. 2F

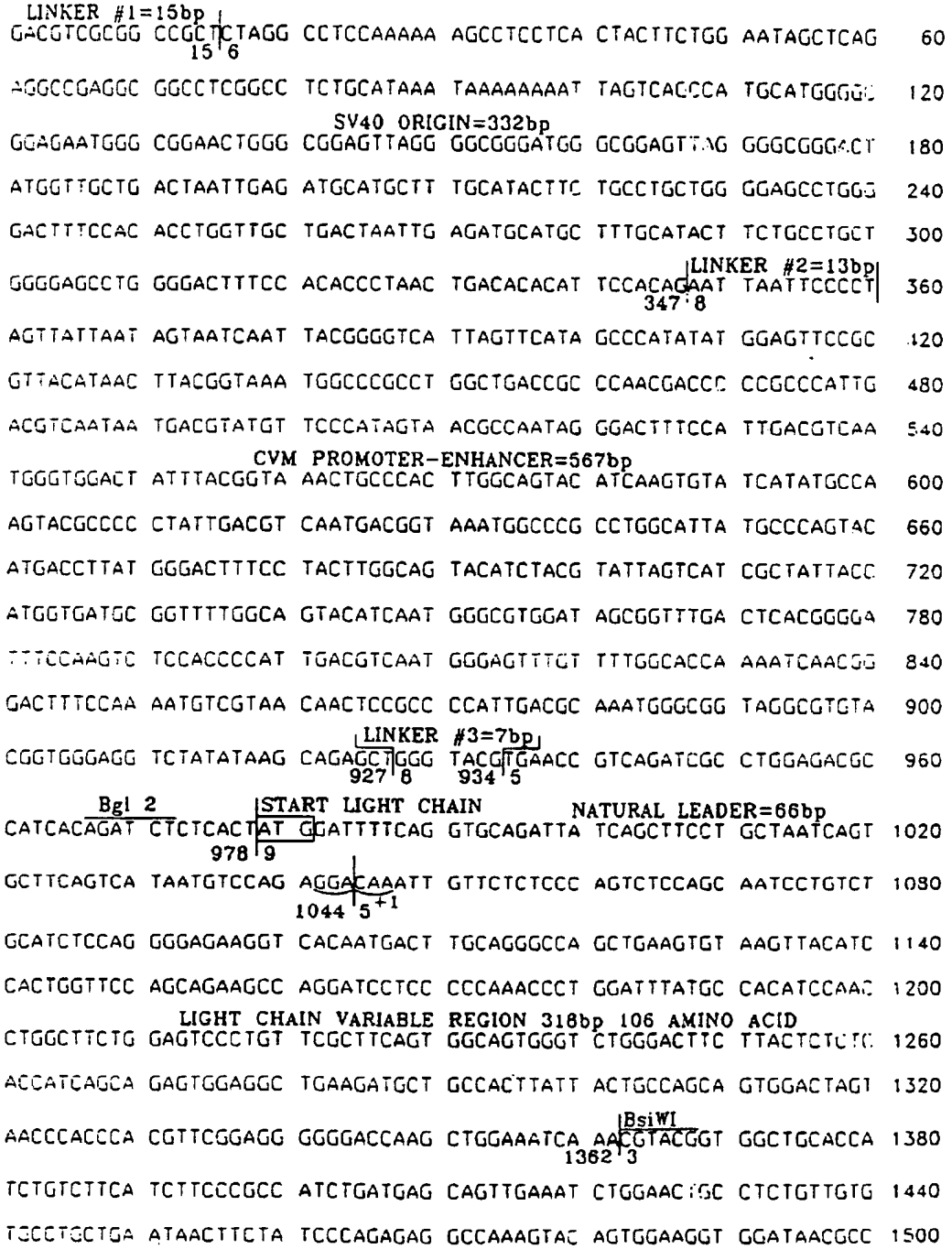

LINKER #1=15bp
15 6
SV40 ORIGIN=332bp
LINKER #2=13bp
347 8
CVM PROMOTER-ENHANCER=567bp
LINKER #3=7bp
927 8
934 5
Bgl 2
START LIGHT CHAIN
NATURAL LEADER=66bp
978 9
1044 5 +1
LIGHT CHAIN VARIABLE REGION 318bp 106 AMINO ACID
BsiWI
1362 3

FIG. 3A

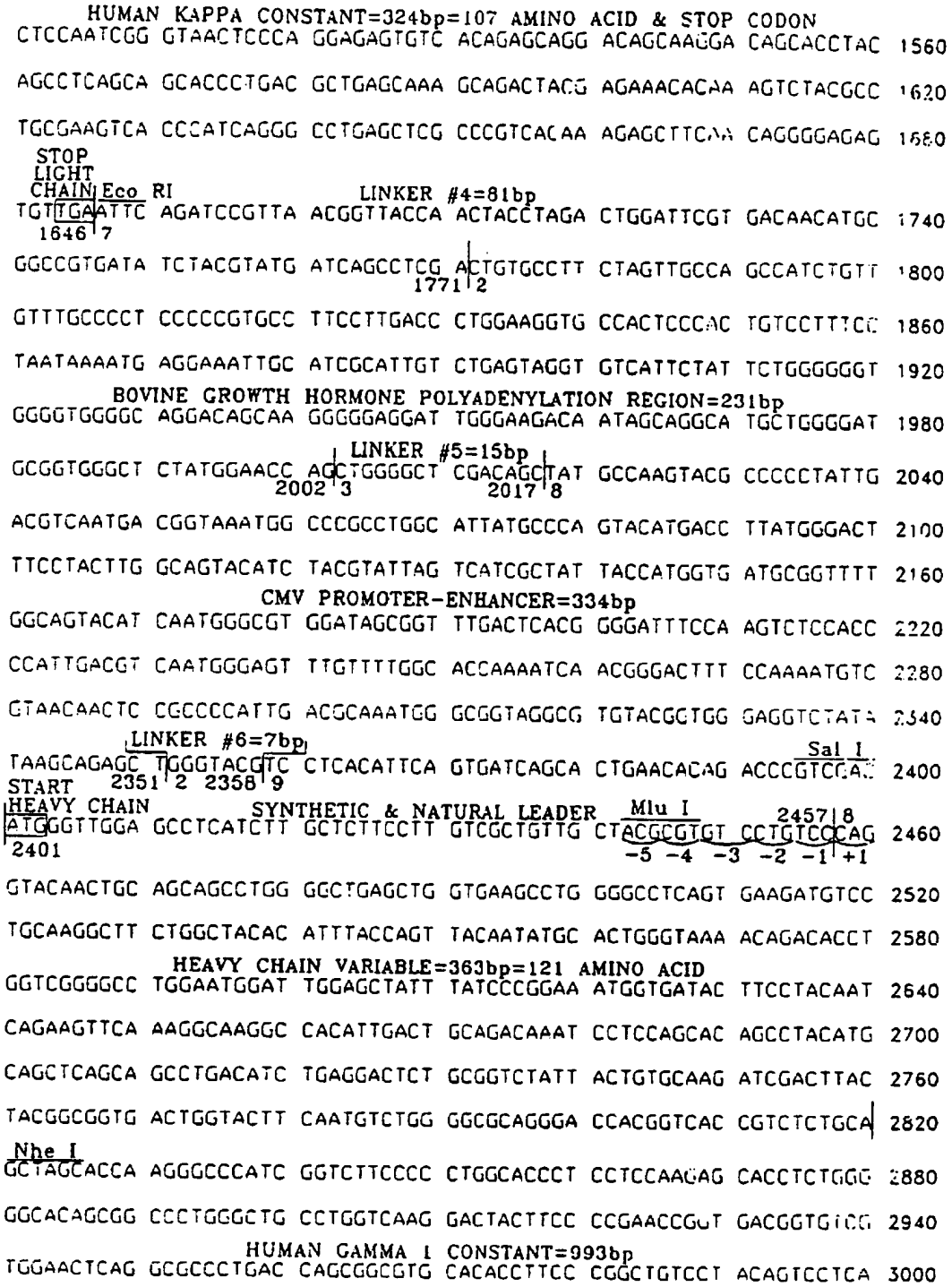

HUMAN KAPPA CONSTANT=324bp=107 AMINO ACID & STOP CODON
CTCCAATCGG GTAACTCCCA GGAGAGTGTC ACAGAGCAGG ACAGCAAGGA CAGCACCTAC 1560
AGCCTCAGCA GCACCCTGAC GCTGAGCAAA GCAGACTACG AGAAACACAA AGTCTACGCC 1620
TGCGAAGTCA CCCATCAGGG CCTGAGCTCG CCCGTCACAA AGAGCTTCAA CAGGGGAGAG 1680
STOP
LIGHT
CHAIN Eco RI
LINKER #4=81bp
TGTTGAATTC AGATCCGTTA ACGGTTACCA ACTACCTAGA CTGGATTCGT GACAACATGC 1740
1646 7
GGCCGTGATA TCTACGTATG ATCAGCCTCG ACTGTGCCTT CTAGTTGCCA GCCATCTGTT 1800
1771 2
GTTTGCCCCT CCCCCGTGCC TTCCTTGACC CTGGAAGGTG CCACTCCCAC TGTCCTTTCC 1860
TAATAAAATG AGGAAATTGC ATCGCATTGT CTGAGTAGGT GTCATTCTAT TCTGGGGGGT 1920
BOVINE GROWTH HORMONE POLYADENYLATION REGION=231bp
GGGGTGGGGC AGGACAGCAA GGGGGAGGAT TGGGAAGACA ATAGCAGGCA TGCTGGGGAT 1980
LINKER #5=15bp
GCGGTGGGCT CTATGGAACC AGCTGGGGCT CGACAGCTAT GCCAAGTACG CCCCCTATTG 2040
2002 3 2017 8
ACGTCAATGA CGGTAAATGG CCCGCCTGGC ATTATGCCCA GTACATGACC TTATGGGACT 2100
TTCCTACTTG GCAGTACATC TACGTATTAG TCATCGCTAT TACCATGGTG ATGCGGTTTT 2160
CMV PROMOTER-ENHANCER=334bp
GGCAGTACAT CAATGGGCGT GGATAGCGGT TTGACTCACG GGGATTTCCA AGTCTCCACC 2220
CCATTGACGT CAATGGGAGT TTGTTTTGGC ACCAAAATCA ACGGGACTTT CCAAAATGTC 2280
GTAACAACTC CGCCCCATTG ACGCAAATGG GCGGTAGGCG TGTACGGTGG GAGGTCTATA 2340
LINKER #6=7bp
Sal I
TAAGCAGAGC TGGGTACGTC CTCACATTCA GTGATCAGCA CTGAACACAG ACCCGTCGAC 2400
START 2351 2 2358 9
HEAVY CHAIN
SYNTHETIC & NATURAL LEADER
Mlu I
2457 8
ATGGGTTGGA GCCTCATCTT GCTCTTCCTT GTCGCTGTTG CTACGCGTGT CCTGTCCCAG 2460
2401
-5 -4 -3 -2 -1 +1
GTACAACTGC AGCAGCCTGG GGCTGAGCTG GTGAAGCCTG GGGCCTCAGT GAAGATGTCC 2520
TGCAAGGCTT CTGGCTACAC ATTTACCAGT TACAATATGC ACTGGGTAAA ACAGACACCT 2580
HEAVY CHAIN VARIABLE=363bp=121 AMINO ACID
GGTCGGGGCC TGGAATGGAT TGGAGCTATT TATCCCGGAA ATGGTGATAC TTCCTACAAT 2640
CAGAAGTTCA AAGGCAAGGC CACATTGACT GCAGACAAAT CCTCCAGCAC AGCCTACATG 2700
CAGCTCAGCA GCCTGACATC TGAGGACTCT GCGGTCTATT ACTGTGCAAG ATCGACTTAC 2760
TACGGCGGTG ACTGGTACTT CAATGTCTGG GGCGCAGGGA CCACGGTCAC CGTCTCTGCA 2820
Nhe I
GCTAGCACCA AGGGCCCATC GGTCTTCCCC CTGGCACCCT CCTCCAAGAG CACCTCTGGG 2880
GGCACAGCGG CCCTGGGCTG CCTGGTCAAG GACTACTTCC CCGAACCGGT GACGGTGTCG 2940
HUMAN GAMMA 1 CONSTANT=993bp
TGGAACTCAG GCGCCCTGAC CAGCGGCGTG CACACCTTCC CGGCTGTCCT ACAGTCCTCA 3000

FIG. 3B

330 AMINO ACID & STOP CODON

```
GGACTCTACT CCCTCAGCAG CGTGGTGACC GTGCCCTCCA GCAGCTTGGG CACCCAGACC 3060
TACATCTGCA ACGTGAATCA CAAGCCCAGC AACACCAAGG TGGACAAGAA AGCAGAGCCC 3120
AAATCTTGTG ACAAAACTCA CACATGCCCA CCGTGCCCAG CACCTGAACT CCTGGGGGGA 3180
CCGTCAGTCT TCCTCTTCCC CCCAAAACCC AAGGACACCC TCATGATCTC CCGGACCCCT 3240
GAGGTCACAT GCGTGGTGGT GGACGTGAGC CACGAAGACC CTGAGGTCAA GTTCAACTGG 3300
TACGTGGACG GCGTGGAGGT GCATAATGCC AAGACAAAGC CGCGGGAGGA GCAGTACAAC 3360
AGCACGTACC GTGTGGTCAG CGTCCTCACC GTCCTGCACC AGGACTGGCT GAATGGCAAG 3420
GAGTACAAGT GCAAGGTCTC CAACAAAGCC CTCCCAGCCC CCATCGAGAA AACCATCTCC 3480
AAAGCCAAAG GGCAGCCCCG AGAACCACAG GTGTACACCC TGCCCCCATC CCGGGATGAG 3540
CTGACCAAGA ACCAGGTCAG CCTGACCTGC CTGGTCAAAG GCTTCTATCC CAGCGACATC 3600
GCCGTGGAGT GGGAGAGCAA TGGGCAGCCG GAGAACAACT ACAAGACCAC GCCTCCCGTG 3660
CTGGACTCCG ACGGCTCCTT CTTCCTCTAC AGCAAGCTCA CCGTGGACAA GAGCAGGTGG 3720
CAGCAGGGGA ACGTCTTCTC ATGCTCCGTG ATGCATGAGG CTCTGCACAA CCACTACACG 3780
```

STOP HEAVY CHAIN | Bam HI LINKER #7=81bp

```
CAGAAGAGCC TCTCCCTGTC TCCGGGTAAA TGAGGATCCG TTAACGGTTA CCAACTACCT 3840
                          3813 | 4
AGACTGGATT CGTGACAACA TGCGGCCGTG ATATCTACGT ATGATCAGCC TCGACTGTGC 3900
                                                    3894 | 5
CTTCTAGTTG CCAGCCATCT GTTGTTTGCC CCTCCCCCGT GCCTTCCTTG ACCCTGGAAG 3960
GTGCCACTCC CACTGTCCTT TCCTAATAAA ATGAGGAAAT TGCATCGCAT TGTCTGAGTA 4020
```

BOVINE GROWTH HORMONE POLYADENYLATION REGION=231bp

```
GGTGTCATTC TATTCTGGGG GGTGGGGTGG GGCAGGACAG CAAGGGGGAG GATTGGGAAG 4080
```

LINKER #8=34bp

```
ACAATAGCAG GCATGCTGGG GATGCGGTGG GCTCTATGGA ACCAG|CTGGG GCTCGACAGC 4140
                                          4125 | 6
GCTGGATCTC CCGATCCCCA GCTTTGCTTC TCAATTTCTT ATTTGCATAA TGAGAAAAAA 4200
AGGAAAATTA ATTTTAACAC CAATTCAGTA GTTGATTGAG CAAATGCGTT GCCAAAAAGG 4260
```

MOUSE BETA GLOBIN MAJOR PROMOTER=366bp

```
ATGCTTTAGA GACAGTGGTC TCTGCACAGA TAAGGACAAA CATTATTCAG AGGGAGTACC 4320
CAGAGCTGAG ACTCCTAAGC CAGTGAGTGG CACAGCATTC TAGGGAGAAA TATGCTTGTC 4380
ATCACCGAAG CCTGATTCCG TAGAGCCACA CCTTGGTAAG GGCCAATCTG CTCACACAGG 4440
ATAGAGAGGG CAGGAGCCAG GGCAGAGCAT ATAAGGTGAG GTAGGATCAG TTGCTCCTCA 4500
```

FIG. 3C

LINKER #9=19bP 5' UNTRANSLATED DHFR=82bp
CATTTGCTTC TGACATAGTT GTGTTGGGAG CTTGGATAGC TTGGACAGCT CAGGGCTGCG 4560
4525 6 4544 5

ATTTCGCGCC AAACTTGACG GCAATCCTAG CGTGAAGGCT GGTAGGATTT TATCCCCGCT 4620

START DHFR
GCCATCATGG TTCGACCATT GAACTGCATC GTCGCCGTGT CCCAAAATAT GGGGATTGGC 4680
4626 7

AAGAACGGAG ACCTACCCTG GCCTCCGCTC AGGAACGAGT TCAAGTACTT CCAAAGAATG 4740

ACCACAACCT CTTCAGTGGA AGGTAAACAG AATCTGGTGA TTATGGGTAG GAAAACCTGG 4800

DHFR=564bp=187 AMINO ACID & STOP CODON
TTCTCCATTC CTGAGAAGAA TCGACCTTTA AAGGACAGAA TTAATATAGT TCTCAGTAGA 4860

GAACTCAAAG AACCACCACG AGGAGCTCAT TTTCTTGCCA AAAGTTTGGA TGATGCCTTA 4920

AGACTTATTG AACAACCGGA ATTGGCAAGT AAAGTAGACA TGGTTTGGAT AGTCGGAGGC 4980

AGTTCTGTTT ACCAGGAAGC CATGAATCAA CCAGGCCACC TTAGACTCTT TGTGACAAGG 5040

ATCATGCAGG AATTTGAAAG TGACACGTTT TTCCCAGAAA TTGATTTGGG GAAATATAAA 5100

CTTCTCCCAG AATACCCAGG CGTCCTCTCT GAGGTCCAGG AGGAAAAAGG CATCAAGTAT 5160

STOP DHFR 3' UNTRANSLATED DHFR=82bp
AAGTTTGAAG TCTACGAGAA GAAAGACTAA CAGGAAGATG CTTTCAAGTT CTCTGCTCCC 5220
5140 1

LINKER #10
CTCCTAAAGC TATGCATTTT TATAAGACCA TGGGACTTTT GCTGGCTTTA GATCAGCCTC 5280
5272 3
=10bp
GACTGTGCCT TCTAGTTGCC AGCCATCTGT TGTTTGCCCC TCCCCCGTGC CTTCCTTGAC 5340

BOVINE GROWTH HORMONE POLYADENYLATION=231bp
CCTGGAAGGT GCCACTCCCA CTGTCCTTTC CTAATAAAAT GAGGAAATTG CATCGCATTG 5400

TCTGAGTAGG TGTCATTCTA TTCTGGGGGG TGGGGTGGGG CAGGACAGCA AGGGGGAGGA 5460

LINKER #11
TTGGGAAGAC AATAGCAGGC ATGCTGGGGA TGCGGTGGGC TCTATGGAAC CAGCTGGGGC 5520
5513 4
=17bp
TCGAGCTACT AGCTTTGCTT CTCAATTTCT TATTTGCATA ATGAGAAAAA AAGGAAAATT 5580
5530 1

AATTTTAACA CCAATTCAGT AGTTGATTGA GCAAATGCGT TGCCAAAAAG GATGCTTTAG 5640

MOUSE BETA GLOBIN MAJOR PROMOTER=366bp
AGACAGTGTT CTCTGCACAG ATAAGGACAA CTAGGGAGAA ATATGCTTGT CATCACCGAA 5700

GACTCCTAAG CCAGTGAGTG GCACAGCATT CTAGGGAGAA ATATGCTTGT CATCACCGAA 5760

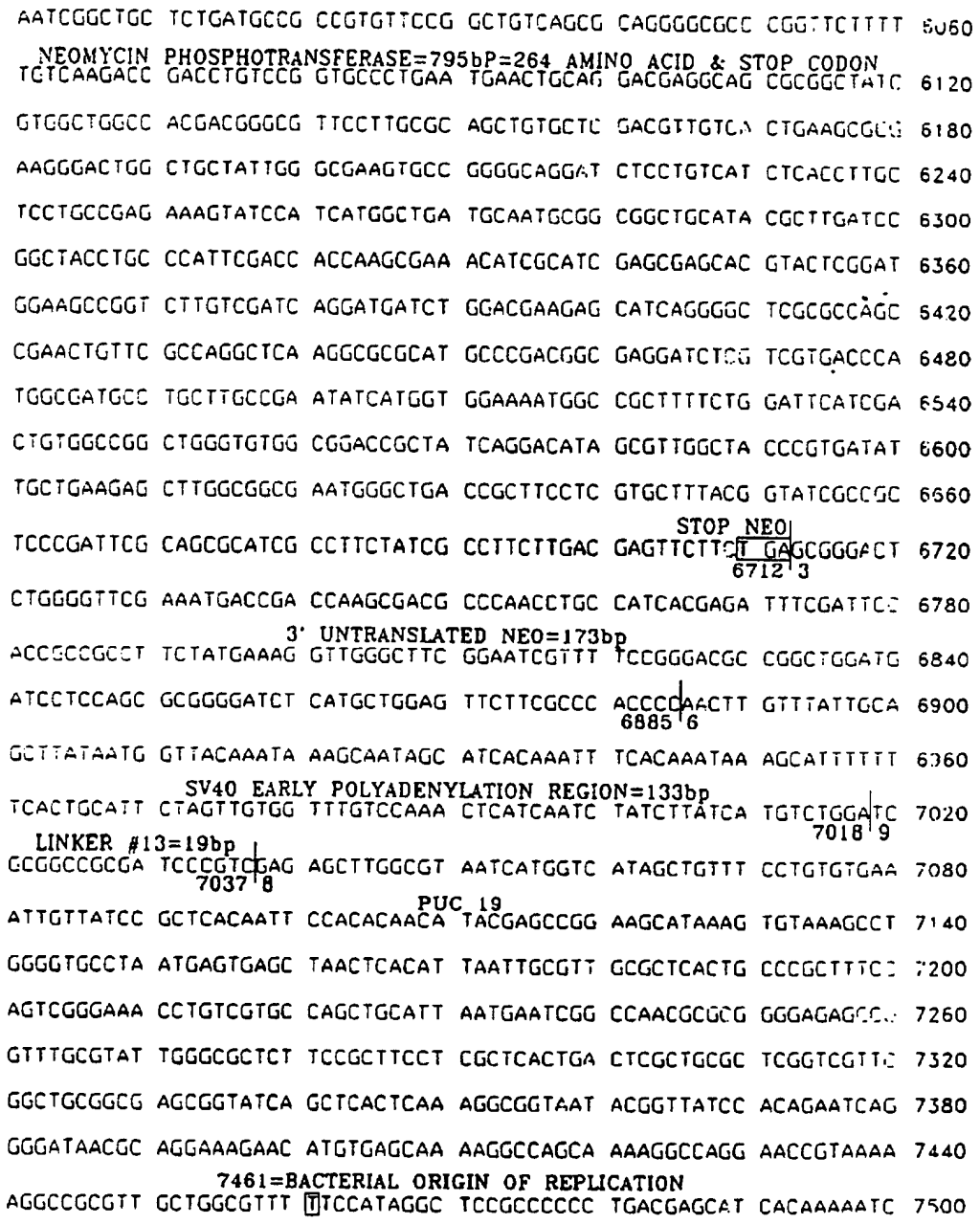
GCCTGATTCC GTAGAGCCAC ACCTTGGTAA GGGCCAATCT GCTCACACAG GATAGAGAGC 5820

GCAGGAGCCA GGGCAGAGCA TATAAGGTGA GGTAGGATCA GTTGCTCCTC ACATTTGCTT 5880

LINKER #12=21bp START NEO
CTGACATAGT TGTGTTGGGA GCTTGGATCG ATCCTCTATG GTTGAACAAG ATGGATTGCA 5940
5896 7 5917 8

CGCAGGTTCT CCGGCCGCTT GGGTGGAGAG GCTATTCGGC TATGACTGGG CACAACAGAC 6000

FIG. 3D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STOP NEO
6712 3
3' UNTRANSLATED NEO=173bp
6885 6
SV40 EARLY POLYADENYLATION REGION=133bp
7018 9
LINKER #13=19bp
7037 8
PUC 19
7461=BACTERIAL ORIGIN OF REPLICATION

FIG. 3E

GACGCTCAAG TCAGAGGTGG CGAAACCCGA CAGGACTATA AAGATACCAG GCGTTTCCCC 7560
CTGGAAGCTC CCTCGTGCGC TCTCCTGTTC CGACCCTGCC GCTTACCGGA TACCTGTCCG 7620
CCTTTCTCCC TTCGGGAAGC GTGGCGCTTT CTCAATGCTC ACGCTGTAGG TATCTCAGTT 7680
CGGTGTAGGT CGTTCGCTCC AAGCTGGGCT GTGTGCACGA ACCCCCCGTT CAGCCCGACC 7740
GCTGCGCCTT ATCCGGTAAC TATCGTCTTG AGTCCAACCC GGTAAGACAC GACTTATCGC 7800
CACTGGCAGC AGCCACTGGT AACAGGATTA GCAGAGCGAG GTATGTAGGC GGTGCTACAG 7860
AGTTCTTGAA GTGGTGGCCT AACTACGGCT ACACTAGAAG GACAGTATTT GGTATCTGCG 7920
CTCTGCTGAA GCCAGTTACC TTCGGAAAAA GAGTTGGTAG CTCTTGATCC GGCAAACAAA 7980
CCACCGCTGG TAGCGGTGGT TTTTTTGTTT GCAAGCAGCA GATTACGCGC AGAAAAAAAG 8040
GATCTCAAGA AGATCCTTTG ATCTTTTCTA CGGGGTCTGA CGCTCAGTGG AACGAAAACT 8100
CACGTTAAGG GATTTTGGTC ATGAGATTAT CAAAAAGGAT CTTCACCTAG ATCCTTTTAA 8160
ATTAAAAATG AAGTTTTAAA TCAATCTAAA GTATATATGA GTAAACTTGG TCTGACAGTT 8220
STOP
BETA LACTAMASE
ACCAATGCTT AATCAGTGAG GCACCTATCT CAGCGATCTG TCTATTTCGT TCATCCATAG 8280
TTGCCTGACT CCCCGTCGTG TAGATAACTA CGATACGGGA GGGCTTACCA TCTGGCCCCA 8340
GTGCTGCAAT GATACCGCGA GACCCACGCT CACCGGCTCC AGATTTATCA GCAATAAACC 8400
BETA LACTAMASE=861bp=286 AMINO ACID & STOP CODON
AGCCAGCCGG AAGGGCCGAG CGCAGAAGTG GTCCTGCAAC TTTATCCGCC TCCATCCAGT 8460
CTATTAATTG TTGCCGGGAA GCTAGAGTAA GTAGTTCGCC AGTTAATAGT TTGCGCAACG 8520
TTGTTGCCAT TGCTACAGGC ATCGTGGTGT CACGCTCGTC GTTTGGTATG GCTTCATTCA 8580
GCTCCGGTTC CCAACGATCA AGGCGAGTTA CATGATCCCC CATGTTGTGC AAAAAAGCGG 8640
TTAGCTCCTT CGGTCCTCCG ATCGTTGTCA GAAGTAAGTT GGCCGCAGTG TTATCACTCA 8700
TGGTTATGGC AGCACTGCAT AATTCTCTTA CTGTCATGCC ATCCGTAAGA TGCTTTTCTG 8760
TGACTGGTGA GTACTCAACC AAGTCATTCT GAGAATAGTG TATGCGGCGA CCGAGTTGCT 8820
CTTGCCCGGC GTCAATACGG GATAATACCG CGCCACATAG CAGAACTTTA AAAGTGCTCA 8880
TCATTGGAAA ACGTTCTTCG GGGCGAAAAC TCTCAAGGAT CTTACCGCTG TTGAGATCCA 8940
GGTCGATGTA ACCCACTCGT GCACCCAACT GATCTTCAGC ATCTTTTACT TTCACCAGCG 9000
TTTCTGGGTG AGCAAAAACA GGAAGGCAAA ATGCCGCAAA AAAGGGAATA AGGGCGACAC 9060
START BETA LACTAMASE
GGAAATGTTG AATACTCATA CTCTTCCTTT TTCAATATTA TTGAAGCATT TATCAGGGTT 9120
ATTGTCTCAT GAGCGGATAC ATATTTGAAT GTATTTAGAA AAATAAACAA ATAGGGGTTC 9180
CGCGCACATT TCCCCGAAAA GTGCCACCT

FIG. 3F

LEADER

-20 -15 -10

FRAME 1 Met Asp Phe Gln Val Gln Ile Ile Ser Phe Leu Leu Ile Ser Ala Ser Val

ATG GAT TTT CAG GTG CAG ATT ATC AGC TTC CTG CTA ATC AGT GCT TCA GTC

987 996 1005 1014 1023

-5 -1 | +1 FR1 10

Ile Met Ser Arg Gly | Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser

ATA ATG TCC AGA GGA | CAA ATT GTT CTC TCC CAG TCT CCA GCA ATC CTG TCT GCA TCT

1038 1047 1056 1065 1074 1083

20 23 | 24 CDR1 27/ 29 30 34 |

Pro Gly Glu Lys Val Thr Met Thr Cys | Arg Ala Ser Ser Ser Val Ser Tyr Ile His |

CCA GGG GAG AAG GTC ACA ATG ACT TGC | AGG GCC AGC TCA AGT GTA AGT TAC ATC CAC |

1095 1104 1113 | 1122 1131 1140 |

35 FR2 40 45 49 | 50 CDR2

Trp Phe Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr | Ala Thr Ser Asn

TGG TTC CAG CAG AAG CCA GGA TCC TCC CCC AAA CCC TGG ATT TAT | GCC ACA TCC AAC

1152 1161 1170 1179 1188 | 1197

55 56 | 57 60 FR3 65 70

Leu Ala Ser | Gly Val Pro Val Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser

CTG GCT TCT | GGA GTC CCT GTT CGC TTC AGT GGC AGT GGG TCT GGG ACT TCT TAC TCT

1209 | 1218 1227 1236 1245 1254

75 80 85 88 | 89 90

Leu Thr Ile Ser Arg Val Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys | Gln Gln Trp

CTC ACC ATC AGC AGA GTG GAG GCT GAA GAT GCT GCC ACT TAT TAC TGC | CAG CAG TGG

1266 1275 1284 1293 1302 | 1311

CDR3 95 97 | 98 100 FR4 105 107 |

Thr Ser Asn Pro Pro Thr | Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys |

ACT AGT AAC CCA CCC ACG | TTC GGA GGG GGG ACC AAG CTG GAA ATC AAA |

1323 1332 | 1341 1350 1359 |

FIG. 4

LEADER

```
                -19                 -15                 -10                  -5
FRAME 1  Met Gly Trp Ser Leu Ile Leu Leu Phe Leu Val Ala Val Ala Thr Arg Val
         ATG GGT TGG AGC CTC ATC TTG CTC TTC CTT GTC GCT GTT GCT ACG CGT GTC
                2409        2418        2427        2436        2445

     -1| +1      FR1                                 10                  15
Leu Ser| Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Ala Gly Ala Ser
CTG TCC| CAG GTA CAA CTG CAG CAG CCT GGG GCT GAG CTG GTG AAG CCT GGG GCC TCA
       2460        2469        2478        2487        2496        2505

          20                  25                  30| 31   CDR1      35 |36
Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr |Ser Tyr Asn Met His |Trp
GTG AAG ATG TCC TGC AAG GCT TCT GGC TAC ACA TTT ACC |AGT TAC AAT ATG CAC |TGG
       2517        2526        2536        2544    |2553        2562|

             40  FR2             45                 49 |50      52 52A  53  54
Val Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile Gly |Ala Ile Tyr Pro Gly Asn
GTA AAA CAG ACA CCT GGT CGG GGC CTG GAA TGG ATT GGA |GCT ATT TAT CCC GGA AAT
       2574        2583        2592        2601    |2610        2619

55          CDR2     60                  65 |66 FR3          70
Gly Asp Thr Ser Tyr Asn Gln Lys Phe Lys Gly |Lys Ala Thr Leu Thr Ala Asp Lys
GGT GAT ACT TCC TAC AAT CAG AAG TTC AAA GGC |AAG GCC ACA TTG ACT GCA GAC AAA
       2631        2640        2649        2658        2667        2676

    75                  80      82  82A 82B 82C 83      85
Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
TCC TCC AGC ACA GCC TAC ATG CAG CTC AGC AGC CTG ACA TCT GAG GAC TCT GCG GTC
       2688        2697        2706        2715        2724        2733

90                94|95      CDR3       100 100A 100B 100C 100D 101 |102 103
Tyr Tyr Cys Ala Arg|Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val| Trp Gly
TAT TAC TGT GCA AGA|TCG ACT TAC TAC GGC GGT GAC TGG TAC TTC AAT GTC| TGG GGC
       2745        2754        2763        2772        2781        2790

105 FR4             110         113|
Ala Gly Thr Thr Val Thr Val Ser Ala|
GCA GGG ACC ACG GTC ACC GTC TCT GCA|
       2802        2811        2820|
```

FIG. 5

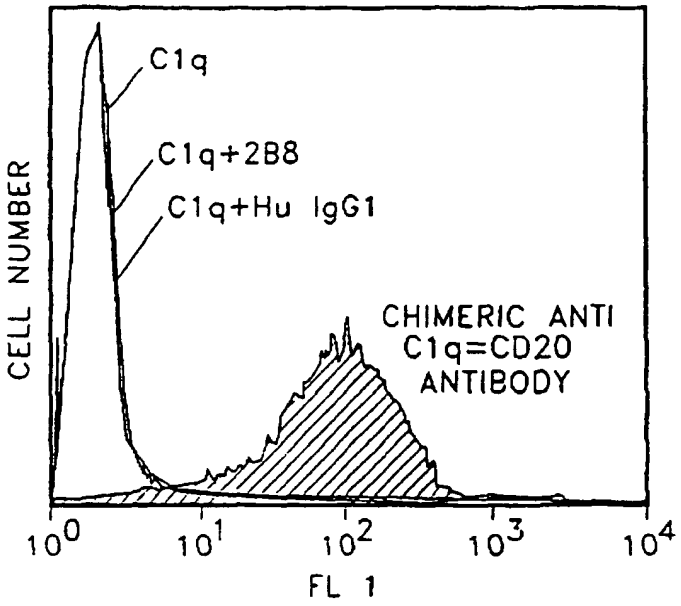
C1q
C1q+2B8
C1q+Hu IgG1
CHIMERIC ANTI C1q=CD20 ANTIBODY
CELL NUMBER
10^0
10^1
10^2
10^3
10^4
FL 1

FIG. 6

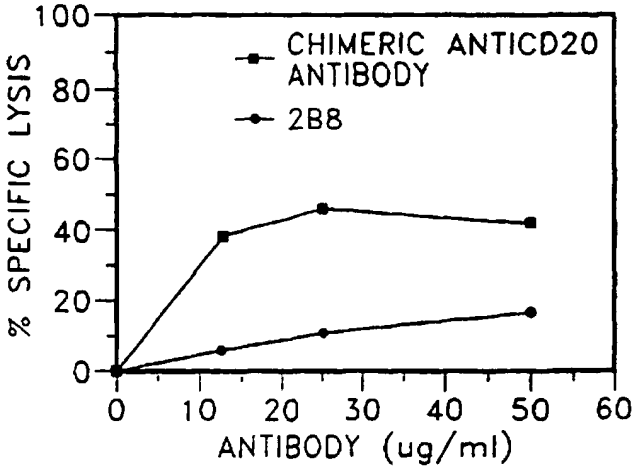
CHIMERIC ANTICD20 ANTIBODY
2B8
% SPECIFIC LYSIS
100
80
60
40
20
0
0
10
20
30
40
50
60
ANTIBODY (ug/ml)

FIG. 7

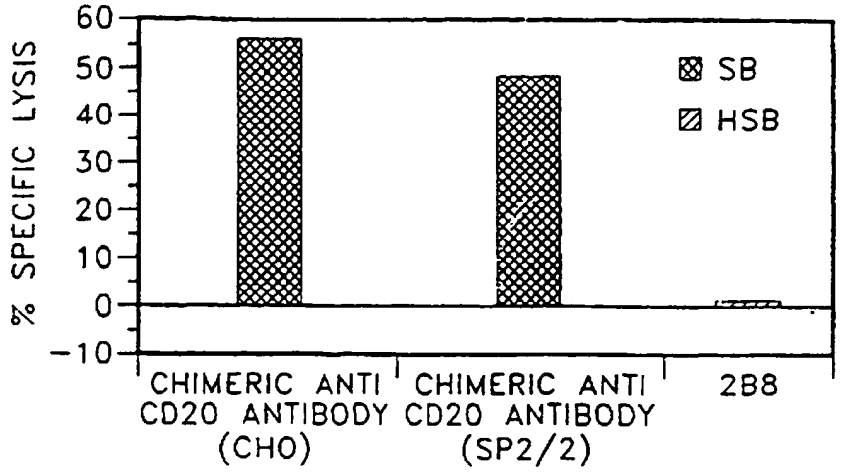
% SPECIFIC LYSIS
60
50
40
30
20
10
0
-10
SB
HSB
CHIMERIC ANTI CD20 ANTIBODY (CHO)
CHIMERIC ANTI CD20 ANTIBODY (SP2/2)
2B8
ANTIBODY

FIG. 8

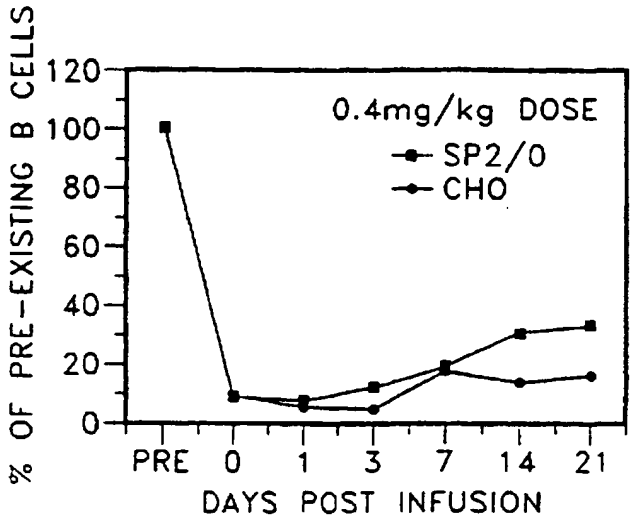
% OF PRE-EXISTING B CELLS
120
100
80
60
40
20
0
0.4mg/kg DOSE
SP2/0
CHO
PRE
0
1
3
7
14
21
DAYS POST INFUSION

FIG. 9A

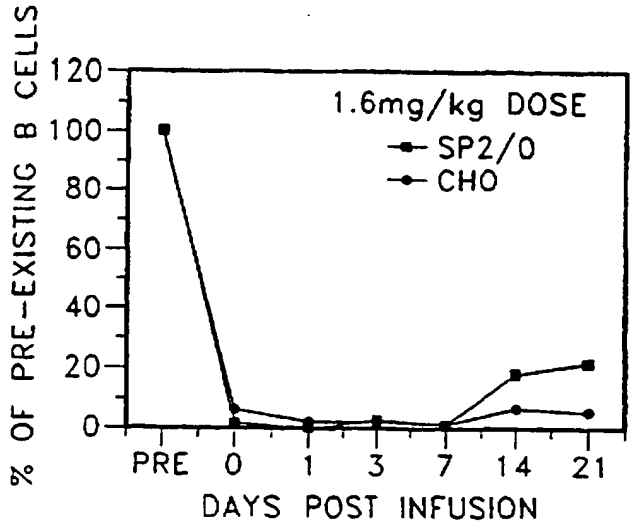
% OF PRE-EXISTING B CELLS
120
100
80
60
40
20
0
1.6mg/kg DOSE
SP2/0
CHO
PRE
0
1
3
7
14
21
DAYS POST INFUSION

FIG. 9B

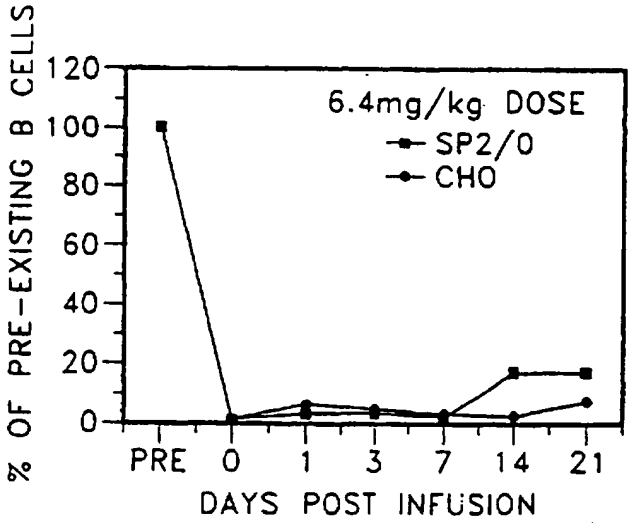
% OF PRE-EXISTING B CELLS
120
100
80
60
40
20
0
6.4mg/kg DOSE
SP2/0
CHO
PRE
0
1
3
7
14
21
DAYS POST INFUSION

FIG. 9C

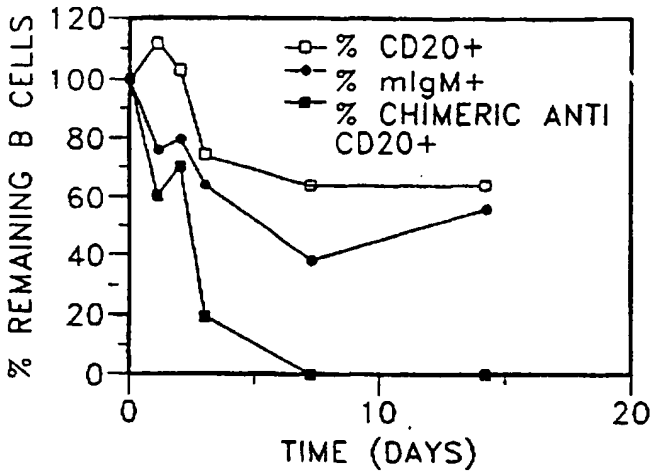
% REMAINING B CELLS
120
100
80
60
40
20
0
0
10
20
TIME (DAYS)
% CD20+
% mIgM+
% CHIMERIC ANTI CD20+

FIG. 10

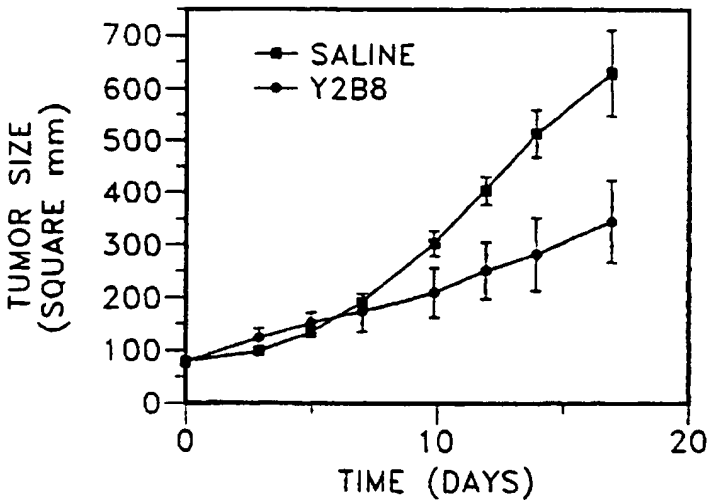
TUMOR SIZE (SQUARE mm)
700
600
500
400
300
200
100
0
0
10
20
TIME (DAYS)
SALINE
Y2B8

FIG. 11

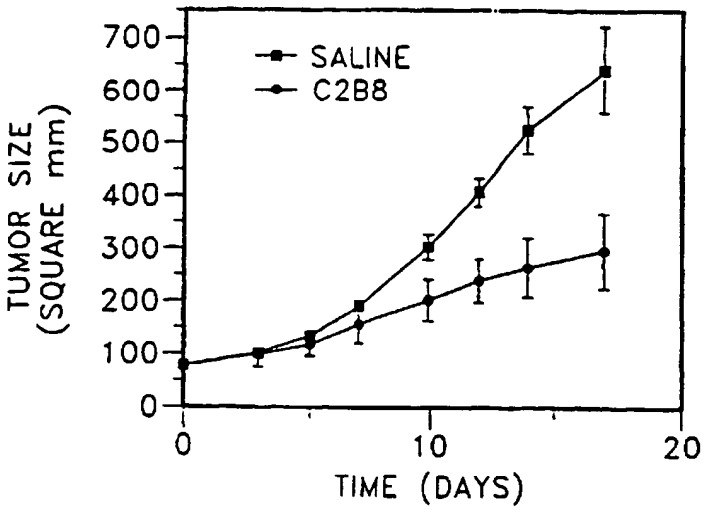
700
600
500
400
300
200
100
0
TUMOR SIZE (SQUARE mm)
SALINE
C2B8
0
10
20
TIME (DAYS)

FIG. 12

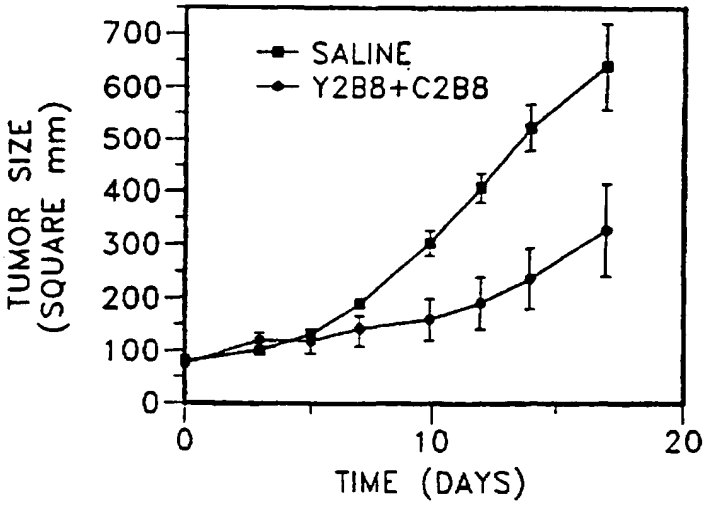
700
600
500
400
300
200
100
0
TUMOR SIZE (SQUARE mm)
SALINE
Y2B8+C2B8
0
10
20
TIME (DAYS)

FIG. 13

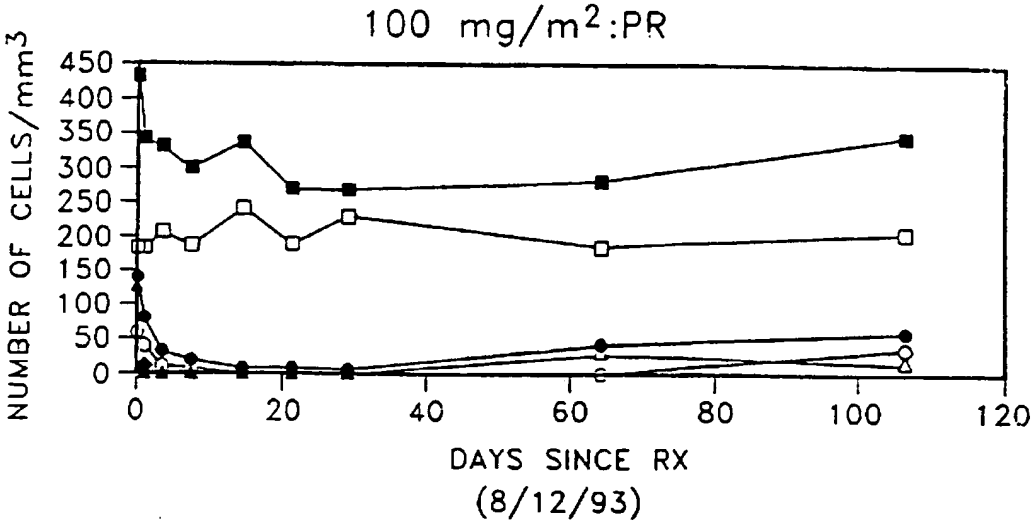

FIG. 14A

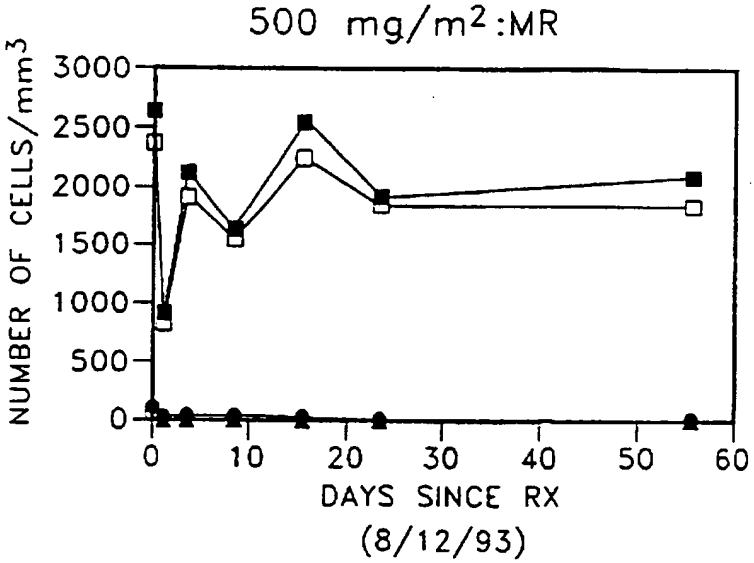

FIG. 14B

THERAPEUTIC APPLICATION OF CHIMERIC AND RADIOLABELED ANTIBODIES TO HUMAN B LYMPHOCYTE RESTRICTED DIFFERENTIATION ANTIGEN FOR TREATMENT OF B CELL LYMPHOMA

This application is a divisional of application Ser. No. 08/149,099, filed Nov. 3, 1993, which is a continuation in part of U.S. application Ser. No. 07/978,891, filed Nov. 13, 1992, now abandoned.

RELATED APPLICATIONS

This patent document is related to United States Serial No. 07/977,691, entitled "IMPAIRED DOMINANT SELECTABLE MARKER SEQUENCE FOR ENHANCEMENT OF EXPRESSION OF CO-LINKED GENE PRODUCT AND EXPRESSION VECTOR SYSTEMS COMPRISING SAME" having U.S. Ser. No. 07/977,691 (now abandoned; filed Nov. 13, 1992) and "IMPAIRED DOMINANT SELECTABLE MARKER SEQUENCE AND INTRONIC INSERTION STRATEGIES FOR ENHANCEMENT OF EXPRESSION OF GENE PRODUCT AND EXPRESSION VECTOR SYSTEMS COMPRISING SAME," U.S. Ser. No. 08/147,696 (filed simultaneously herewith) now U.S. Pat. No. 5,648,267. The related patent documents are incorporated herein by reference.

TABLE OF CONTENTS

A. FIELD OF THE INVENTION

The references to be discussed throughout this document are set forth merely for the information described therein prior to the filing dates of this document, and nothing herein is to be construed as an admission, either express or implied, that the references are "prior art" or that the inventors are not entitled to antedate such descriptions by virtue of prior inventions or priority based on earlier filed applications.

The present invention is directed to the treatment of B cell lymphoma using chimeric and radiolabeled antibodies to the B cell surface antigen Bp35 ("CD20").

B. BACKGROUND OF THE INVENTION

The immune system of vertebrates (for example, primates, which include humans, apes, monkeys, etc.) consists of a number of organs and cell types which have evolved to: accurately and specifically recognize foreign microorganisms ("antigen") which invade the vertebrate-host; specifically bind to such foreign microorganisms; and, eliminate/destroy such foreign microorganisms. Lymphocytes, amongst others, are critical to the immune system. Lymphocytes are produced in the thymus, spleen and bone marrow (adult) and represent about 30% of the total white blood cells present in the circulatory system of humans (adult). There are two major sub-populations of lymphocytes: T cells and B cells. T cells are responsible for cell mediated immunity, while B cells are responsible for antibody production (humoral immunity). However, T cells and B cells can be considered as interdependent—in a typical immune response, T cells are activated when the T cell receptor binds to fragments of an antigen that are bound to major histocompatability complex ("MHC") glycoproteins on the surface of an antigen presenting cell; such activation causes release of biological mediators ("interleukins") which, in essence, stimulate B cells to differentiate and produce antibody ("immunoglobulins") against the antigen.

Each B cell within the host expresses a different antibody on its surface—thus, one B cell will express antibody specific for one antigen, while another B cell will express

antibody specific for a different antigen. Accordingly, B cells are quite diverse, and this diversity is critical to the immune system. In humans, each B cell can produce an enormous number of antibody molecules (ie. about 10^7 to 10^8). Such antibody production most typically ceases (or substantially decreases) when the foreign antigen has been neutralized. Occasionally, however, proliferation of a particular B cell will continue unabated; such proliferation can result in a cancer referred to as "B cell lymphoma."

T cells and B cells both comprise cell surface proteins which can be utilized as "markers" for differentiation and identification. One such human B cell marker is the human B lymphocyte-restricted differentiation antigen Bp35, referred to as "CD20." CD20 is expressed during early pre-B cell development and remains until plasma cell differentiation. Specifically, the CD20 molecule may regulate a step in the activation process which is required for cell cycle initiation and differentiation and is usually expressed at very high levels on neoplastic ("tumor") B cells. CD20, by definition, is present on both "normal" B cells as well as "malignant" B cells, ie, those B cells whose unabated proliferation can lead to B cell lymphoma. Thus, the CD20 surface antigen has the potential of serving as a candidate for "targeting" of B cell lymphomas.

In essence, such targeting can be generalized as follows: antibodies specific to the CD20 surface antigen of B cells are, eg, injected into a patient. These anti-CD20 antibodies specifically bind to the CD20 cell surface antigen of (ostensibly) both normal and malignant B cells; the anti-CD20 antibody bound to the CD20 surface antigen may lead to the destruction and depletion of neoplastic B cells. Additionally, chemical agents or radioactive labels having the potential to destroy the tumor can be conjugated to the anti-CD20 antibody such that the agent is specifically "delivered" to eg, the neoplastic B cells. Irrespective of the approach, a primary goal is to destroy the tumor: the specific approach can be determined by the particular anti-CD20 antibody which is utilized and, thus, the available approaches to targeting the CD20 antigen can vary considerably.

For example, attempts at such targeting of CD20 surface antigen have been reported. Murine (mouse) monoclonal antibody 1F5 (an anti-CD20 antibody) was reportedly administered by continuous intravenous infusion to B cell lymphoma patients. Extremely high levels (>2 grams) of 1F5 were reportedly required to deplete circulating tumor cells, and the results were described as being "transient." Press et al., "Monoclonal Antibody 1F5 (Anti-CD20) Serotherapy of Human B-Cell Lymphomas." *Blood* 69/2:584–591 (1987). A potential problem with this approach is that non-human monoclonal antibodies (eg, murine monoclonal antibodies) typically lack human effector functionality, ie, they are unable to, inter alia, mediate complement dependent lysis or lyse human target cells through antibody dependent cellular toxicity or Fc-receptor mediated phagocytosis. Furthermore, non-human monoclonal antibodies can be recognized by the human host as a foreign protein; therefore, repeated injections of such foreign antibodies can lead to the induction of immune responses leading to harmful hypersensitivity reactions. For murine-based monoclonal antibodies, this is often referred to as a Human Anti-Mouse Antibody response, or "HAMA" response. Additionally, these "foreign" antibodies can be attacked by the immune system of the host such that they are, in effect, neutralized before they reach their target site. Lymphocytes and lymphoma cells are inherently sensitive to radiotherapy for several reasons: the local emission of ionizing radiation of radiolabeled antibodies may kill cells with or without the target antigen (eg, CD20) in close proximity to antibody bound to the antigen; penetrating radiation may obviate the problem of limited access to the antibody in bulky or poorly vascularized tumors; and, the total amount of antibody required may be reduced. The radionuclide emits radioactive particles which can damage cellular DNA to the point where the cellular repair mechanisms are unable to allow the cell to continue living; therefore, if the target cells are tumors, the radioactive label beneficially kills the tumor cells. Radiolabeled antibodies, by definition, include the use of a radioactive substance which may require the need for precautions for both the patient (ie, possible bone marrow transplantation) as well as the health care provider (ie, the need to exercise a high degree of caution when working with the radioactivity).

Therefore, an approach at improving the ability of murine monoclonal antibodies to be effective in the treatment of B-cell disorders has been to conjugate a radioactive label or toxin to the antibody such that the label or toxin is localized at the tumor site. For example, the above-referenced 1F5 antibody has been "labeled" with iodine-131 ("131I") and was reportedly evaluated for biodistribution in two patients. See Eary, J. F. et al., "Imaging and Treatment of B-Cell Lymphoma" *J. Nuc. Med.* 31/8:1257–1268 (1990); see also, Press, O. W. et al., "Treatment of Refractory Non-Hodgkin's Lymphoma with Radiolabeled MB-1 (Anti-CD37) Antibody" *J. Clin. Onc.* 7/8:1027–1038 (1989) (indication that one patient treated with ^{131}I-labeled IF-5 achieved a "partial response"); Goldenberg, D. M. et al., "Targeting, Dosimetry and Radioimmunotherapy of B-Cell Lymphomas with Iodine-131-Labeled LL2 Monoclonal Antibody" *J. Clin. Onc.* 9/4:548–564 (1991) (three of eight patients receiving multiple injections reported to have developed a HAMA response); Appelbaum, F. R. "Radiolabeled Monoclonal Antibodies in the Treatment of Non-Hodgkin's Lymphoma" *Hem./Onc. Clinics of N. A.* 5/5:1013–1025 (1991) (review article); Press, O. W. et al "Radiolabeled-Antibody Therapy of B-Cell Lymphoma with Autologous Bone Marrow Support." *New England Journal of Medicine* 329/17: 1219–12223 (1993) (iodine-131 labeled anti-CD20 antibody IF5 and B1); and Kaminski, M. G. et al "Radioimmunotherapy of B-Cell Lymphoma with [^{131}I] Anti-B1 (Anti-CD20) Antibody". NEJM329/7(1993) (iodine-131 labeled anti-CD20 antibody B1; hereinafter "Kaminski").

Toxins (ie, chemotherapeutic agents such as doxorubicin or mitomycin C) have also been conjugated to antibodies. See, for example, PCT published application WO 92/07466 (published May 14, 1992).

"Chimeric" antibodies, ie, antibodies which comprise portions from two or more different species (eg, mouse and human) have been developed as an alternative to "conjugated" antibodies. For example, Liu, A. Y. et al, "Production of a Mouse-Human Chimeric Monoclonal Antibody to CD20 with Potent Fc-Dependent Biologic Activity" *J. Immun.* 139/10:3521–3526 (1987), describes a mouse/human chimeric antibody directed against the CD20 antigen. See also, PCT Publication No. WO 88/04936. However, no information is provided as to the ability, efficacy or practicality of using such chimeric antibodies for the treatment of B cell disorders in the reference. It is noted that in vitro functional assays (eg, complement dependent lysis ("CDC"); antibody dependent cellular cytotoxicity ("ADCC"), etc.) cannot inherently predict the in vivo capability of a chimeric antibody to destroy or deplete target cells expressing the specific antigen. See, for example, Robinson, R. D. et al., "Chimeric mouse-human anti-carcinoma anti-

bodies that mediate different anti-tumor cell biological activities." *Hum. Antibod. Hybridomas* 2:84–93 (1991) (chimeric mouse-human antibody having undetectable ADCC activity). Therefore, the potential therapeutic efficacy of chimeric antibody can only truly be assessed by in vivo experimentation.

What is needed, and what would be a great advance in the art, are therapeutic approaches targeting the CD20 antigen for the treatment of B cell lymphomas in primates, including, but not limited to, humans.

C. SUMMARY OF THE INVENTION

Disclosed herein are therapeutic methods designed for the treatment of B cell disorders, and in particular, B cell lymphomas. These protocols are based upon the administration of immunologically active chimeric anti-CD20 antibodies for the depletion of peripheral blood B cells, including B cells associated with lymphoma; administration of radiolabeled anti-CD20 antibodies for targeting localized and peripheral B cell associated tumors; and administration of chimeric anti-CD20 antibodies and radiolabeled anti-CD20 antibodies in a cooperative therapeutic strategy.

D. BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a diagrammatic representation of a tandem chimeric antibody expression vector useful in the production of immunologically active chimeric anti-CD20 antibodies ("TCAE 8");

FIGS. 2A through 2E (SEQ ID NO: 1) are the nucleic acid sequence of the vector of FIG. 1;

FIGS. 3A through 3F (SEQ ID NO: 2) are the nucleic acid sequence of the vector of FIG. 1 further comprising murine light and heavy chain variable regions ("anti-CD20 in TCAE 8");

FIG. 4 is the nucleic acid and amino acid sequences (including CDR and framework regions) of murine variable region light chain derived from murine anti-CD20 monoclonal antibody 2B8 (SEQ ID NO: 3–4);

FIG. 5 is the nucleic acid and amino acid sequences (including CDR and framework regions) of murine variable region heavy chain derived from murine anti-CD20 monoclonal antibody 2B8 (SEQ ID NO: 5–6);

FIG. 6 are flow cytometry results evidencing binding of fluorescent-labeled human Clq to chimeric anti-CD20 antibody, including, as controls labeled Clq; labeled Clq and murine anti-CD20 monoclonal antibody 2B8; and labeled Clq and human IgG1.k;

FIG. 7 represents the results of complement related lysis comparing chimeric anti-CD20 antibody and murine anti-CD20 monoclonal antibody 2B8;

FIG. 8 represents the results of antibody mediated cellular cytotoxicity with it in vivo human effector cells comparing chimeric anti-CD20 antibody and 2B8;

FIG. 9A, 9B and 9C provide the results of non-human primate peripheral blood B lymphocyte depletion after infusion of 0.4 mg/kg (A); 1.6 mg/kg (B); and 6.4 mg/kg (C) of immunologically active chimeric anti-CD20 antibody;

FIG. 10 provides the results of, inter alia, non-human primate peripheral blood B lymphocyte depletion after infusion of 0.01 mg/kg of immunologically active chimeric anti-CD20 antibody;

FIG. 11 provides results of the tumoricidal impact of Y2B8 in a mouse xenographic model utilizing a B cell lymphoblastic tumor;

FIG. 12 provides results of the tumoricidal impact of C2B8 in a mouse xenographic model utilizing a B cell lymphoblastic tumor;

FIG. 13 provides results of the tumoricidal impact of a combination of Y2B8 and C2B8 in a mouse xenographic model utilizing a B cell lymphoblastic tumor; and

FIGS. 14A and 14B provide results from a Phase I/II clinical analysis of C2B8 evidencing B-cell population depletion over time for patients evidencing a partial remission of the disease (14A) and a minor remission of the disease (14B).

E. DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Generally, antibodies are composed of two light chains and two heavy chain molecules; these chains form a general "Y" shape, with both light and heavy chains forming the arms of the Y and the heavy chains forming the base of the Y. Light and heavy chains are divided into domains of structural and functional homology. The variable domains of both the light ("V_L") and the heavy ("V_H") chains determine recognition and specificity. The constant region domains of light ("C_L") and heavy ("C_H") chains confer important biological properties, eg antibody chain association, secretion, transplacental mobility, Fc receptor binding complement binding, etc. The series of events leading to immunoglobulin gene expression in the antibody producing cells are complex. The variable domain region gene sequences are located in separate germ line gene segments referred to as "V_H," "D," and "J_H," or "V_L" and "J_L." These gene segments are joined by DNA rearrangements to form the complete V regions expressed in heavy and light chains, respectively. The rearranged, joined V segments (V_L-J_L and V_H-D-J_H) then encode the complete variable regions or antigen binding domains of light and heavy chains, respectively.

Serotherapy of human B cell lymphomas using an anti-CD20 murine monoclonal antibody (1F5) has been described by Press et al., (69 *Blood* 584, 1987, supra); the reported therapeutic responses, unfortunately, were transient. Additionally, 25% of the tested patients reportedly developed a human anti-mouse antibody (HAMA) response to the serotherapy. Press et al., suggest that these antibodies, conjugated to toxins or radioisotopes, might afford a more lasting clinical benefit than the unconjugated antibody.

Owing to the debilitating effects of B cell lymphoma and the very real need to provide viable treatment approaches to this disease, we have embarked upon different approaches having a particular antibody, 2B8, as the common link between the approaches. One such approach advantageously exploits the ability of mammalian systems to readily and efficiently recover peripheral blood B cells; using this approach, we seek to, in essence, purge or deplete B cells in peripheral blood and lymphatic tissue as a means of also removing B cell lymphomas. We accomplish this by utilization of, inter alia, immunologically active, chimeric anti-CD20 antibodies. In another approach, we seek to target tumor cells for destruction with radioactive labels.

As used herein, the term "anti-CD20 antibody" is an antibody which specifically recognizes a cell surface non-glycosylated phosphoprotein of 35,000 Daltons, typically designated as the human B lymphocyte restricted differentiation antigen Bp35, commonly referred to as CD20. As used herein, the term "chimeric" when used in reference to anti-CD20 antibodies, encompasses antibodies which are most preferably derived using recombinant deoxyribo-

nucleic acid techniques and which comprise both human (including immunologically "related" species, eg. chimpanzee) and non-human components: the constant region of the chimeric antibody is most preferably substantially identical to the constant region of a natural human antibody; the variable region of the chimeric antibody is most preferably derived from a non-human source and has the desired antigenic and specificity to the CD20 cell surface antigen. The non-human source can be any vertebrate source which can be used to generate antibodies to a human CD20 cell surface antigen or material comprising a human CD20 cell surface antigen. Such non-human source includes, but is not limited to, rodents (eg. rabbit, rat, mouse, etc.) and non-human primates (eg. Old World Monkey, Ape, etc.). Most preferably, the non-human component (variable region) is derived from a murine source. As used herein, the phrase "immunologically active" when used in reference to chimeric anti-CD20 antibodies, means a chimeric antibody which binds human Clq, mediates complement dependent lysis ("CDC") of human B lymphoid cell lines, and lyses human target cells through antibody dependent cellular cytotoxicity ("ADCC"). As used herein, the phrases "indirect labeling" and "indirect labeling approach" both mean that a chelating agent is covalently attached to an antibody and at least one radionuclide is inserted into the chelating agent. Preferred chelating agents and radionuclides are set forth in Srivagtava, S. C. and Mease, R. C., "Progress in Research on Ligands, Nuclides and Techniques for Labeling Monoclonal Antibodies," *Nucl. Med. Bio.* 18/6: 589–603 (1991) ("Srivagtava") which is incorporated herein by reference. A particularly preferred chelating agent is 1-isothiocycmatobenzyl-3-methyldiothelene triaminepent acetic acid ("MX—DTPA"); particularly preferred radionuclides for indirect labeling include indium [111] and yttrium [90]. As used herein, the phrases "direct labeling" and "direct labeling approach" both mean that a radionuclide is covalently attached directly to an antibody (typically via an amino acid residue). Preferred radionuclides are provided in Srivagtava; a particularly preferred radionuclide for direct labeling is iodine [131] covalently attached via tyrosine residues. The indirect labeling approach is particularly preferred.

The therapeutic approaches disclosed herein are based upon the ability of the immune system of primates to rapidly recover, or rejuvenate, peripheral blood B cells. Additionally, because the principal immune response of primates is occasioned by T cells, when the immune system has a peripheral blood B cell deficiency, the need for "extraordinary" precautions (ie, patient isolation, etc.) is not necessary. As a result of these and other nuances of the immune systems of primates, our therapeutic approach to B cell disorders allows for the purging of peripheral blood B cells using immunologically active chimeric anti-CD20 antibodies.

Because peripheral blood B cell disorders, by definition, can indicate a necessity for access to the blood for treatment, the route of administration of the immunologically active chimeric anti-CD20 antibodies and radioalabeled anti-CD20 antibodies is preferably parenteral; as used herein, the term "parenteral" includes intravenous, intramuscular, subcutaneous, rectal, vaginal or intraperitoneal administration. Of these, intravenous administration is most preferred.

The immunologically active chimeric anti-CD20 antibodies and radiolabeled anti-CD20 antibodies will typically be provided by standard technique within a pharmaceutically acceptable buffer, for example, sterile saline, sterile buffered water, propylene glycol, combinations of the foregoing, etc. Methods for preparing parenterally administerable agents are described in *Pharmaceutical Carriers & Formulations*, Martin, Remington's Pharmaceutical Sciences, 15th Ed. (Mack Pub. Co., Easton, Pa. 1975), which is incorporated herein by reference.

The specific, therapeutically effective amount of immunologically active chimeric anti-CD20 antibodies useful to produce a unique therapeutic effect in any given patient can be determined by standard techniques well known to those of ordinary skill in the art.

Effective dosages (ie, therapeutically effective amounts) of the immunologically active chimeric anti-CD20 antibodies range from about 0.001 to about 30 mg/kg body weight, more preferably from about 0.01 to about 25 mg/kg body weight, and most preferably from about 0.4 to about 20.0 mg/kg body weight. Other dosages are viable; factors influencing dosage include, but are not limited to, the severity of the disease; previous treatment approaches; overall health of the patient; other diseases present, etc. The skilled artisan is readily credited with assessing a particular patient and determining a suitable dosage that falls within the ranges, or if necessary, outside of the ranges.

Introduction of the immunologically active chimeric anti-CD20 antibodies in these dose ranges can be carried out as a single treatment or over a series of treatments. With respect to chimeric antibodies, it is preferred that such introduction be carried out over a series of treatments; this preferred approach is predicated upon the treatment methodology associated with this disease. While not wishing to be bound by any particular theory, because the immunologically active chimeric anti-CD20 antibodies are both immunologically active and bind to CD20, upon initial introduction of the immunologically active chimeric anti-CD20 antibodies to the individual, peripheral blood B cell depletion will begin; we have observed a nearly complete depletion within about 24 hours post treatment infusion. Because of this, subsequent introduction(s) of the immunologically active chimeric anti-CD20 antibodies (or radiolabeled anti-CD20 antibodies) to the patient is presumed to: a) clear remaining peripheral blood B cells; b) begin B cell depletion from lymph nodes; c) begin B cell depletion from other tissue sources, eg, bone marrow, tumor, etc. Stated again, by using repeated introductions of the immunologically active chimeric anti-CD20 antibodies, a series of events take place, each event being viewed by us as important to effective treatment of the disease. The first "event" then, can be viewed as principally directed to substantially depleting the patient's peripheral blood B cells; the subsequent "events" can be viewed as either principally directed to simultaneously or serially clearing remaining B cells from the system clearing lymph node B cells, or clearing other tissue B cells.

In effect, while a single dosage provides benefits and can be effectively utilized for disease treatment/management, a preferred treatment course can occur over several stages; most preferably, between about 0.4 and about 20 mg/kg body weight of the immunologically active chimeric anti-CD20 antibodies is introduced to the patient once a week for between about 2 to 10 weeks, most preferably for about 4 weeks.

With reference to the use of radiolabeled anti-CD20 antibodies, a preference is that the antibody is non-chimeric; this preference is predicted upon the significantly longer circulating half-life of chimeric antibodies vis-a-vis murine antibodies (ie, with a longer circulating half-life, the radionuclide is present in the patient for extended periods).

However, radiolabeled chimeric antibodies can be beneficially utilized with lower milli-Curries ("mCi") dosages used in conjunction with the chimeric antibody relative to the murine antibody. This scenario allows for a decrease in bone marrow toxicity to an acceptable level, while maintaining therapeutic utility.

A variety of radionuclides are applicable to the present invention and those skilled in the art are credited with the ability to readily determine which radionuclide is most appropriate under a variety of circumstances. For example, iodine [131] is a well known radionuclide used for targeted immunotherapy. However, the clinical usefulness of iodine [131] can be limited by several factors including: eight-day physical half-life; dehalogenation of iodinated antibody both in the blood and at tumor sites; and emission characteristics (eg, large gamma component) which can be suboptimal for localized dose deposition in tumor. With the advent of superior chelating agents, the opportunity for attaching metal chelating groups to proteins has increased the opportunities to utilize other radionuclides such as indium [131] and yttrium [90]. Yttrium [90] provides several benefits for utilization in radioimmunotherapeutic applications: the 64 hour half-life of yttrium [90] is long enough to allow antibody accumulation by tumor and, unlike eg, iodine [131], yttrium [901] is a pure beta emitter of high energy with no accompanying gamma irradiation in its decay, with a range in tissue of 100 to 1000 cell diameters. Furthermore, the minimal amount of penetrating radiation allows for outpatient administration of yttrium [90]-labeled antibodies. Additionally, interalization of labeled antibody is not required for cell killing, and the local emission of ionizing radiation should be lethal for adjacent tumor cells lacking the target antigen.

One non-therapeutic limitation to yttrium [90] is based upon the absence of significant gamma radiation making imaging therewith difficult. To avoid this problem, a diagnostic "imaging" radionuclide, such as indium [111], can be utilized for determining the location and relative size of a tumor prior to the administration of therapeutic does of yttrium [90]-labeled anti-CD20. Indium [111] is particularly preferred as the diagnostic radionuclide because: between about 1 to about 10 mCi can be safely administered without detectable toxicity; and the imaging data is generally predictive of subsequent yttrium [90]-labeled antibody distribution. Most imaging studies utilize 5 mCi indium [111]-labeled antibody because this dose is both safe and has increased imaging efficiency compared with lower doses, with optimal imaging occurring at three to six days after antibody administration. See, for example, Murray J. L., 26 *J. Nuc. Med.* 3328 (1985) and Carraguillo, J. A. et al. 26 *J. Nuc. Med* 67 (1985).

Effective single treatment dosages (ie, therapeutically effective amounts) of yttrium [90] labeled anti-CD20 antibodies range from between about 5 and about 75 mCi, more preferably between about 10 and about 40 mCi. Effective single treatment non-marrow ablative dosages of iodine [131] labeled anti-CD20 antibodies range from between about 5 and about 70 mCi, more preferably between about 5 and about 40 mCi. Effective single treatment ablative dosages (ie, may require autologous bone marrow transplantation) of iodine [131] labeled anti-CD20 antibodies range from between about 30 and about 600 mCi, more preferably between about 50 and less than about 500 mCi. In conjunction with a chimeric anti-CD20 antibody, owing to the longer circulating half life vis-a-vis murine antibodies, an effective single treatment non-marrow ablative dosages of iodine [131] labeled chimeric anti-CD20 antibodies range from between about 5 and about 40 mCi, more preferably less than about 30 mCi. Imaging criteria for, eg, the indium [111] label, are typically less than about 5 mCi.

With respect to radiolabeled anti-CD20 antibodies, therapy therewith can also occur using a single therapy treatment or using multiple treatments. Because of the radionuclide component, it is preferred that prior to treatment, peripheral stem cells ("PSC") or bone marrow ("BM") be "harvested" for patients experiencing potentially fatal bone marrow toxicity resulting from radiation. BM and/or PSC are harvested using standard techniques, and then purged and frozen for possible reinfusion. Additionally, it is most preferred that prior to treatment a diagnostic dosimetry study using a diagnostic labeled antibody (eg, using indium [111]) be conducted on the patient, a purpose of which is to ensure that the therapeutically labeled antibody (eg, using yttrium [90]) will not become unnecessarily "concentrated" in any normal organ or tissue.

Chimeric mouse/human antibodies have been described. See, for example, Morrison, S. L. et al., *PNAS* 1:6851–6854 (November 1984); European Patent Publication No. 173494; Boulianne, G. L. et al., *Nature* 312:643 (December 1984); Neubeiger, M. S. et al., *Nature* 314:268 (March 1985); European Patent Publication No. 125023; Tan et al., *J. Immunol.* 135:8564 (November 1985); Sun, L. K. et al., *Hybridoma* 5/1:517 (1986); Sahagan et al., *J. Immunol.* 137:1066–1074 (1986). See generally, Muron, *Nature* 312:597 (December 1984); Dickson, *Genetic Engineering News* 5/3 (March 1985); Marx, *Science* 229 455 (August 1985); and Morrison *Science* 229:1202–1207 (September 1985). Robinson et al., in PCT Publication Number WO 88/04936 describe a chimeric antibody with human constant region and murine variable region, having specificity to an epitope of CD20; the murine portion of the chimeric antibody of the Robinson references is derived from the 2H7 mouse monoclonal antibody (gamma 2b, kappa). While the reference notes that the described chimeric antibody is a "prime candidate" for the treatment of B cell disorders, this statement can be viewed as no more than a suggestion to those in the art to determine whether or not this suggestion is accurate for this particular antibody, particularly because the reference lacks any data to support an assertion of therapeutic effectiveness, and importantly, data using higher order mammals such as primates or humans.

Methodologies for generating chimeric antibodies are available to those in the art. For example, the light and heavy chains can be expressed separately, using, for example, immunoglobulin light chain and immunoglobulin heavy chains in separate plasmids. These can then be purified and assembled in vitro into complete antibodies; methodologies for accomplishing such assembly have been described. See, for example, Scharff, M., *Harvey Lectures* 69:125 (1974). In vitro reaction parameters for the formation of IgG antibodies from reduced isolated light and heavy chains have also been described. See, for example, Beychok, S., *Cells of Immunoglobulin Synthesis*, Academic Press, New York, p. 69, 1979. Co-expression of light and heavy chains in the same cells to achieve intracellular association and linkage of heavy and light chains into complete H_2L_2 IgG antibodies is also possible. Such co-expression can be accomplished using either the same or different plasmids in the same host cell.

Another approach, and one which is our most preferred approach for developing a chimeric non-human/human anti-CD20 antibody, is based upon utilization of an expression vector which includes, ab initio, DNA encoding heavy and light chain constant regions from a human source. Such a

vector allows for inserting DNA encoding non-human variable region such that a variety of non-human anti-CD20 antibodies can be generated, screened and analyzed for various characteristics (eg. type of binding specificity, epitope binding regions, etc.); thereafter, cDNA encoding the light and heavy chain variable regions from a preferred or desired anti-CD20 antibody can be incorporated into the vector. We refer to these types of vectors as Tandem Chimeric Antibody Expression ("TCAE") vectors. A most preferred TCAE vector which was used to generate immunologically active chimeric anti-CD20 antibodies for therapeutic treatment of lymphomas is TCAE 8. TCAE 8 is a derivative of a vector owned by the assignee of this patent document, referred to as TCAE 5.2 the difference being that in TCAE 5.2, the translation initiation start site of the dominant selectable marker (neomycin phosphostransferase, "NEO") is a consensus' Kozak sequence, while for TCAE 8, this region is a partially impaired consensus Kozak sequence. Details regarding the impact of the initiation start site of the dominant selectable marker of the TCAE vectors (also referred to as "ANEX vector") vis-a-vis protein expression are disclosed in detail in the co-pending application filed herewith.

TCAE 8 comprises four (4) transcriptional cassettes, and these are in tandem order, ie, a human immunoglobulin light chain absent a variable region; a human immunoglobulin heavy chain absent a variable region; DHFR; and NEO. Each transcriptional cassette contains its own eukaryotic promoter and polyadenylation region (reference is made to FIG. 1 which is a diagrammatic representation of the TCAE 8 vector (SEQ ID NO: 1–2). Specifically:

1) the CMV promoter/enhancer in front of the immunoglobulin heavy chain is a truncated version of the promoter/enhancer in front of the light chain, from the Nhe I site at −350 to the Sst I site at −16 (see, 41 *Cell* 521, 1985).

2) a human immunoglobulin light chain constant region was derived via amplification of cDNA by a PCR reaction. In TCAE 8, this was the human immunoglobulin light chain kappa constant region (Kabat numbering, amino acids 108–214, allotype Km 3, (see, Kabat, E. A. "Sequences of proteins of immunological interest," NIH Publication, Fifth Ed. No. 91-3242, 1991)), and the human immunoglobulin heavy chain gamma 1 constant region (Kabat numbering amino acids 114–478, allotype Gmla, Gmlz). The light chain was isolated from normal human blood (IDEC Pharmaceuticals Corporation, La Jolla, Calif.); RNA therefrom was used to synthesize cDNA which was then amplified using PCR techniques (primers were derived vis-a-vis the consensus from Kabat). The heavy chain was isolated (using PCR techniques) from cDNA prepared from RNA which was in turn derived from cells transfected with a human IgG1 vector (see, 3 *Prot. Eng.* 531, 1990; vector $pN_{\gamma 1}62$). Two amino acids were changed in the isolated human IgG1 to match the consensus amino acid sequence from Kabat, to wit: amino acid **225** was changed from valine to alanine (GTT to GCA), and amino acid **287** was changed from methionine to lysine (ATG to AAG);

3) The human immunoglobulin light and heavy chain cassettes contain synthetic signal sequences for secretion of the immunoglobulin chains;

4) The human immunoglobulin light and heavy chain cassettes contain specific DNA restriction sites which allow for insertion of light and heavy immunoglobulin variable regions which maintain the transitional reading frame and do not alter the amino acids normally found in immunoglobulin chains;

5) The DHFR cassette contained its own eukaryotic promoter (mouse beta globin major promoter, "BETA") and polyadenylation region (bovine growth hormone polyadenylation, "BGH"); and

6) The NEO cassette contained its own eukaryotic promoter (BETA) and polyadenylation region (SV40 early polyadenylation, "SV").

With respect to the TCAE 8 vector and the NEO cassette, the Kozak region was a partially impaired consensus Kozak sequence (SEQ ID NO: 7) (which included an upstream Cla I site):

	ClaI	−3		+1	
GGGAGCTTGG	ATCGAT	ccTct	ATG	Gtt	(SEQ. ID. NO.7)

(In the TCAE 5.2 vector, the change is between the ClaI and ATG regions, to wit: ccAcc.)

The complete sequence listing of TCAE 8 (including the specific components of the four transcriptional cassettes) is set forth in FIG. 2 SEQ. ID. NO. 1.

As will be appreciated by those in the art, the TCAE vectors beneficially allow for substantially reducing the time in generating the immunologically active chimeric anti-CD20 antibodies. Generation and isolation of non-human light and heavy chain variable regions, followed by incorporation thereof within the human light chain constant transcriptional cassette and human heavy chain constant transcriptional cassette, allows for production of immunologically active chimeric anti-CD20 antibodies.

We have derived a most preferred non-human variable region with specificity to the CD20 antigen using a murine source and hybridoma technology. Using polymerase chain reaction ("PCR") techniques, the murine light and heavy variable regions were cloned directly into the TCAE 8 vector—this is the most preferred route for incorporation of the non-human variable region into the TCAE vector. This preference is principally predicated upon the efficiency of the PCR reaction and the accuracy of insertion. However, other equivalent procedures for accomplishing this task are available. For example, using TCAE 8 (or an equivalent vector), the sequence of the variable region of a non-human anti-CD20 antibody can be obtained, followed by oligonucleotide synthesis of portions of the sequence or, if appropriate, the entire sequence, thereafter, the portions or the entire synthetic sequence can be inserted into the appropriate locations within the vector. Those skilled in the art are credited with the ability to accomplish this task.

Our most preferred immunologically active chimeric anti-CD20 antibodies were derived from utilization of TCAE 8 vector which included murine variable regions derived from monoclonal antibody to CD20; this antibody (to be discussed in detail, infra), is referred to as "2B8." The complete sequence of the variable regions obtained from 2B8 in TCAE 8 ("anti-CD20 in TCAE 8") is set forth in FIG. 3 SEQ. ID. NO. 2.

The host cell line utilized for protein expression is most preferably of mammalian origin; those skilled in the art are credited with ability to preferentially determine particular host cell lines which are best suited for the desired gene product to be expressed therein. Exemplary host cell lines include, but are not limited to, DG44 and DUXBll (Chinese Hamster Ovary lines, DHFR minus), HELA (human cervical carcinoma), CVI (monkey kidney line), COS (a derivative of CVI with SV40 T antigen), R1610 (Chinese hamster

fibroblast) BALBC/3T3 (mouse fibroblast), HAK (hamster kidney line), SP2/0 (mouse myeloma), P3×63-Ag3.653 (mouse myeloma), BFA-lclBPT (bovine endothelial cells), RAJI (human lymphocyte) and 293 (human kidney). Host cell lines are typically available from commercial services, the American Tissue Culture Collection or from published literature.

Preferably the host cell line is either DG44 ("CHO") or SP2/0. See Urland, G. et al., "Effect of gamma rays and the dihydrofolate reductase locus: deletions and inversions." *Som. Cell & Mol. Gen.* 12/6:555–566 (1986), and Shulman, M. et al., "A better cell line for making hybridomas secreting specific antibodies." *Nature* 276:269 (1978), respectively. Most preferably, the host cell line is DG44. Transfection of the plasmid into the host cell can be accomplished by any technique available to those in the art. These include, but are not limited to, transfection (including electrophoresis and electroporation), cell fusion with enveloped DNA, microinjection, and infection with intact virus. See, Ridgway, A. A. G. "Mammalian Expression Vectors." Chapter 24.2, pp. 470–472 *Vectors*, Rodriguez and Denhardt, Eds. (Butterworths, Boston, Mass. 1988). Most preferably, plasmid introduction into the host is via electroporation.

F. EXAMPLES

The following examples are not intended, nor are they to be construed, as limiting the invention. The examples are intended to evidence; dose-imaging using a radiolabeled anti-CD20 antibody ("I2B8"); radiolabeled anti-CD20 antibody ("Y2B8"); and immunologically active, chimeric anti-CD20 antibody ("C2B8") derived utilizing a specific vector ("TCAE 8") and variable regions derived from murine anti-CD20 monoclonal antibody ("2B8").

I. RADIOLABELED ANTI-CD20 ANTIBODY 2B8

A. Anti-CD20 Monoclonal Antibody (Murine) Production ("2B8")

BALB/C mice were repeatedly immunized with the human lymphoblastoid cell line SB (see, Adams, R. A. et al., "Direct implantation and serial transplantation of human acute lymphoblastic leukemia in hamsters, SB-2." *Can Res* 28:1121–1125 (1968); this cell line is available from the American Tissue Culture Collection, Rockville, Md., under ATCC accession number ATCC CCL 120), with weekly injections over a period of 3–4 months. Mice evidencing high serum titers of anti-CD20 antibodies, as determined by inhibition of known CD20-specific antibodies (anti-CD20 antibodies utilized were Leu 16, Beckton Dickinson, San Jose, Calif., Cat. No. 7670; and B1, Coulter Corp., Hialeah, Fla., Cat. No. 6602201) were identified; the spleens of such mice were then removed. Spleen cells were fused with the mouse myeloma SP2/0 in accordance with the protocol described in Einfeld, D. A. et al., (1988) *EMBO* 7:711 (SP2/0 has ATCC accession no. ATCC CRL 8006).

Assays for CD20 specificity were accomplished by radioimmunoassay. Briefly, purified anti-CD20 B1 was radiolabeled with I^{125} by the iodobead method as described in Valentine, M. A. et al., (1989) *J. Biol. Chem.* 264:11282. (I^{125} Sodium Iodide, ICN, Irvine, Calif., Cat. No. 28665H). Hybridomas were screened by co-incubation of 0.05 ml of media from each of the fusion wells together with 0.05 ml of I^{125} labeled anti-CD20 B1 (10 ng) in 1% BSA, PBS (pH 7.4), and 0.5 ml of the same buffer containing 100,000 SB cells. After incubation for 1 hr at room temperature, the cells were harvested by transferring to 96 well titer plates (V&P Scientific, San Diego, Calif.), and washed thoroughly. Duplicate wells containing unlabeled anti-CD20 B1 and wells containing no inhibiting antibody were used as positive and negative controls, respectively. Wells containing greater than 50% inhibition were expanded and cloned. The antibody demonstrating the highest inhibition was derived from the cloned cell line designated herein as "2B8."

B. Preparation of2B8-MX—DTPA Conjugate

i. MX—DTPA

Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid ("carbon-14 labeled MX—DTPA") was used as a chelating agent for conjugation of radiolabel to 2B8. Manipulations of Mx—DTPA were conducted to maintain metal-free conditions, ie, metal-free reagents were utilized and, when possible, polypropylene plastic containers (flasks, beakers, graduated cylinders, pipette tips) washed with ALCONOX® (a detergent) and washed with MILLI-Q® water (purified water), were similarly utilized. MX—DTPA was obtained as a dry solid from Dr. Otto Gansow (National Institute of Health, Bethesda, Md.) and stored desiccated at 4° C. (protected from light), with stock solutions being prepared in MILLI-Q® water at a concentration of 2–5 mM, with storage at −70° C. MX—DTPA was also obtained from Coulter Immunology (Hialeah, Fla.) as the disodium salt in water and stored at −70° C.

ii. Preparation of 2B8

Purified 2B8 was prepared for conjugation with MX—DTPA by transferring the antibody into metal-free 50 mM bicine-NaOff, pH 8.6, containing 150 mM NaCl, using repetitive buffer exchange with CENTRICON 30™ spin filters (30,000D, MWCO; Amicon). Generally, 50–200 μL of protein (10 mg/ml) was added to the filter unit, followed by 2 mL of bicine buffer. The filter was centrifuged at 4° C. in a Sorval SS-34 rotor (6,000 rpm, 45 min.). Retentate volume was approximately 50–100 μL; this process was repeated twice using the same filter. Retentate was transferred to a polypropylene 1.5 mL screw cap tube, assayed for protein, diluted to 10.0 mg/mL and stored at 4° C. until utilized; protein was similarly transferred into 50 mM sodium citrate, pH 5.5, containing 150 mM NaCl and 0.05% sodium azide, using the foregoing protocol.

iii. Conjugation of 2B8 with MX—DTPA

Conjugation of 2B8 with MX—DTPA was performed in polypropylene tubes at ambient temperature. Frozen MX—DTPA stock solutions were thawed immediately prior to use. 50–200 mL of protein at 10 mg/mL were reacted with MX—DTPA at a molar ratio of MX—DTPA-to-2B8 of 4:1. Reactions were initiated by adding the MX—DTPA stock solution and gently mixing; the conjugation was allowed to proceed overnight (14 to 20 hr), at ambient temperature. Unreacted MX—DTPA was removed from the conjugate by dialysis or repetitive ultrafiltration, as described above in Example I.B.ii, into metal-free normal saline (0.9% w/v) containing 0.05% sodium azide. The protein concentration was adjusted to 10 mg/mL and stored at 4° C. in a polypropylene tube until radiolabeled.

iv. Determination of MX—DTPA Incorporation

MX—DTPA incorporation was determined by scintillation counting and comparing the value obtained with the purified conjugate to the specific activity of the carbon-[14]-labeled MX—DTPA. For certain studies, in which non-radioactive MX—DTPA (Coulter Immunology) was utilized, MX—DTPA incorporation was assessed by incubating the conjugate with an excess of a radioactive carrier solution of yttrium-[90] of known concentration and specific activity.

A stock solution of yttrium chloride of known concentration was prepared in metal-free 0.05 N HCl to which carrier-free yttrium-[90] (chloride salt) was added. An aliquot of this solution was analyzed by liquid scintillation counting to determine an accurate specific activity for this reagent. A volume of the yttrium chloride reagent equal to 3-times the number of mols of chelate expected to be attached to the antibody. (typically 2 mol/mol antibody), was added to a polypropylene tube, and the pH adjusted to 4.0–4.5 with 2M sodium acetate. Conjugated antibody was subsequently added and the mixture incubated 15–30 min. at ambient temperature. The reaction was quenched by adding 20 mM EDTA to a final concentration of 1 mM and the pH of the solution adjusted to approximately pH 6 with 2M sodium acetate.

After a 5 min. incubation, the entire volume was purified by high-performance, size-exclusion chromatography (described infra). The eluted protein-containing fractions were combined, the protein concentration determined, and an aliquot assayed for radioactivity. The chelate incorporation was calculated using the specific activity of the yttrium-[90] chloride preparation and the protein concentration.

v. Immunoreactivitv of 2B8-MX—DTPA

The immunoreactivity of conjugated 2B8 was assessed using whole-cell ELISA. Mid-log phase SB cells were harvested from culture by centrifugation and washed two times with 1X HBSS. Cells were diluted to $1–2\times10^6$ cells/mL in HBSS and aliquoted into 96-well polystyrene microtiter plates at 50,000–100,000 cells/well. The plates were dried under vacuum for 2 h. at 40°–45° C. to fix the cells to the plastic; plates were stored dry at −20° C. until utilized. For assay, the plates were warmed to ambient temperature immediately before use, then blocked with 1X PBS, pH 7.2–7.4 containing 1% BSA (2 h). Samples for assay were diluted in 1X PBS/1% BSA, applied to plates and serially diluted (1:2) into the same buffer. After incubating plates for 1 h. at ambient temperature, the plates were washed three times with 1X PBS. Secondary antibody (goat anti-mouse IgG1-specific HRP conjugate 50 μL) was added to wells (1:1500 dilution in 1X PBS/1% BSA) and incubated 1 h. at ambient temperature. Plates were washed four times with 1X PBS followed by the addition of ABTS substrate solution (50 mM sodium citrate, pH 4.5 containing 0.01% ATBS and 0.001% H_2O_2). Plates were read at 405 nm after 15–30 min. incubation. Antigen-negative HSB cells were included in assays to monitor non-specific binding. Immunoreactivity of the conjugate was calculated by plotting the absorbance values vs. the respective dilution factor and comparing these to values obtained using native antibody (representing 100% immunoreactivity) tested on the same plate; several values on the linear portion of the titration profile were compared and a mean value determined (data not shown).

vi. Preparation of Indium-[111]-Labeled 2B8-MX—DTPA ("I2B8")

Conjugates were radiolabeled with carrier-free indium-[111]. An aliquot of isotope (0.1–2 mCi/mg antibody) in 0.05M HCl was transferred to a polypropylene tube and approximately one-tenth volume of metal-free 2M HCl added. After incubation for 5 min., metal-free 2M sodium acetate was added to adjust the solution to pH 4.0–4.4. Approximately 0.5 mg of 2B8-MX—DTPA was added from a stock solution of 10.0 mg/mL DTPA in normal saline, or 50 mM sodium citrate/150 mM NaCl containing 0.05% sodium azide, and the solution gently mixed immediately. The pH solution was checked with pH paper to verify a value of 4.0–4.5 and the mixture incubated at ambient temperature for 15–30 min. Subsequently, the reaction was quenched by adding 20 mM EDTA to a final concentration of 1 mM and the reaction mixture was adjusted to approximately pH 6.0 using 2M sodium acetate.

After a 5–10 min. incubation, uncomplexed radioisotope was removed by size-exclusion chromatography. The HPLC unit consisted of Waters Model 6000 or TosoHaas Model TSK-6110 solvent delivery system fitted, respectively, with a Waters U6K or Rheodyne 700 injection valve. Chromatographic separations were performed using a gel permeation column (BioRad SEC-250; 7.5×300 mm or comparable TosoHaas column) and a SEC-250 guard column (7.5×100 mm). The system was equipped with a fraction collector (Pharmacia Frac200) and a UV monitor fitted with a 280 nm filter (Pharmacia model UV-1). Samples were applied and eluted isocratically using 1X PBS, pH 7.4, at 1.0 mL/min flow rate. One-half milliliter fractions were collected in glass tubes and aliquots of these counted in a gamma counter. The lower and upper windows were set to 100 and 500 KeV respectively.

The radioincorporation was calculated by summing the radioactivity associated with the eluted protein peak and dividing this number by the total radioactivity eluted from the column; this value was then expressed as a percentage (data not shown). In some cases, the radioincorporation was determined using instant thin-layer chromatography ("ITLC"). Radiolabeled conjugate was diluted 1:10 or 1:20 in 1X PBS containing or 1X PBS/1 mM DTPA, then 1 μL was spotted 1.5 cm from one end of a 1×5 cm strip of ITLC SG paper. The paper was developed by ascending chromatography using 10% ammonium acetate in methanol:water (1:1;v/v). The strip was dried, cut in half crosswise, and the radioactivity associated with each section determined by gamma counting. The radioactivity associated with the bottom half of the strip (protein-associated radioactivity) was expressed as a percentage of the total radioactivity, determined by summing the values for both top and bottom halves (data not shown).

Specific activities were determined by measuring the radioactivity of an appropriate aliquot of the radiolabeled conjugate. This value was corrected for the counter efficiency (typically 75%) and related to the protein concentration of the conjugate, previously determined by absorbance at 280 nm, and the resulting value expressed as mCi/mg protein.

For some experiments, 2B8-MX—DTPA was radiolabeled with indium [111] following a protocol similar to the one described above but without purification by HPLC; this was referred to as the "mix-and-shoot" protocol.

vii. Preparation of Yttrium-[90]-Labeled 2B8-MX—DTPA ("Y2B8")

The same protocol described for the preparation of I2B8 was followed for the preparation of the yttrium-[90]-labeled 2B8-MX—DTPA ("Y2B8") conjugate except that 2 ng HCl was not utilized; all preparations of yttrium-labeled conjugates were purified by size-exclusion chromatography as described above.

C. Non-Human Animal Studies.

i. Biodistribution of Radiolabeled 2B8-MX—DTPA

I2B8 was evaluated for tissue biodistribution in six-to-eight week old BALB/c mice. The radiolabeled conjugate was prepared using clinical-grade 2B8-MX—DTPA following the "mix and shoot" protocol described above. The specific activity of the conjugate was 2.3 mCi/mg and the conjugate was formulated in PBS, pH 7.4 containing 50 mg/mL HSA. Mice were injected intravenously with 100 μL of I2B8 (approximately 21 μCi) and groups of three mice were sacrificed by cervical dislocation at 0, 24, 48, and 72

hours. After sacrifice, the tail, heart, lungs, liver, kidney, spleen, muscle, and femur were removed, washed and weighed; a sample of blood was also removed for analysis. Radioactivity associated with each specimen was determined by gamma counting and the percent injected dose per gram tissue subsequently determined. No attempt was made to discount the activity contribution represented by the blood associated with individual organs.

In a separate protocol, aliquots of 2B8-MX—DTPA incubated at 4° C. and 30° C. for 10 weeks were radiolabeled with indium-[111] to a specific activity of 2.1 mCi/mg for both preparations. These conjugates were then used in biodistribution studies in mice as described above.

For dosimetry determinations, 2B8-MX—DTPA was radiolabeled with indium-[111] to a specific activity of 2.3 mCi/mg and approximately 1.1 μCi was injected into each of 20 BALB/c mice. Subsequently, groups of five mice each were sacrificed at 1, 24, 48 and 72 hours and their organs removed and prepared for analysis. In addition, portions of the skin, muscle and bone were removed and processed for analysis; the urine and feces were also collected and analyzed for the 24–72 hour time points.

Using a similar approach, 2B8-MX—DTPA was also radiolabeled with yttrium-[90] and its biological distribution evaluated in BALB/c mice over a 72-hour time period. Following purification by HPLC size exclusion chromatography, four groups of five mice each were injected intravenously with approximately 1 μCi of clinically-formulated conjugate (specific activity:12.2 μCi/mg); groups were subsequently sacrificed at 1, 24, 48 and 72 hours and their organs and tissues analyzed as described above. Radioactivity associated with each tissue specimen was determined by measuring bremstrahlung energy with a gamma scintillation counter. Activity values were subsequently expressed as percent injected dose per gram tissue or percent injected dose per organ. While organs and other tissues were rinsed repeatedly to remove superficial blood, the organs were not perfused. Thus, organ activity values were not discounted for the activity contribution represented by internally associated blood.

ii. Tumor Localization of I2B8

The localization of radiolabeled 2B8-MX—DTPA was determined in athymic mice bearing Ramos B cell tumors. Six-to-eight week old athymic mice were injected subcutaneously (left-rear flank) with 0.1 mL of RPMI-1640 containing 1.2–107 Ramos tumor cells which had been previously adapted for growth in athymic mice. Tumors arose within two weeks and ranged in weight from 0.07 to 1.1 grams. Mice were injected intravenously with 100 μL of indium-[111]-labeled 2B8-MX—DTPA (16.7 μCi) and groups of three mice were sacrificed by cervical dislocation at 0, 24, 48, and 72 hours. After sacrifice the tail, heart, lungs, liver, kidney, spleen, muscle, femur, and tumor were removed, washed, weighed; a sample of blood was also removed for analysis. Radioactivity associated with each specimen was determined by gamma counting and the percent injected dose per gram tissue determined.

iii. Biodistribution and Tumor Localization Studies with Radiolabeled 2B8-MX—DTPA

Following the preliminary biodistribution experiment described above (Example I.B.viii.a.), conjugated 2B8 was radiolabeled with indium-[111] to a specific activity of 2.3 mCi/mg and roughly 1.1 μCi was injected into each of twenty BALB/c mice to determine biodistribution of the radiolabeled material. Subsequentially, groups of five mice each were sacrificed at 1, 24, 48 and 72 hours and their organs and a portion of the skin, muscle and bone were removed and processed for analysis. In addition, the urine and feces were collected and analyzed for the 24–72 hour time-points. The level of radioactivity in the blood dropped from 40.3% of the injected dose per gram at 1 hour to 18.9% at 72 hours (data not shown). Values for the heart, kidney, muscle and spleen remained in the range of 0.7–9.8% throughout the experiment. Levels of radioactivity found in the lungs decreased from 14.2% at 1 hour to 7.6% at 72 hours; similarly the respective liver injected-dose per gram values were 10.3% and 9.9%. These data were used in determining radiation absorbed dose estimates I2B8 described below.

The biodistribution of yttrium-[90]-labeled conjugate, having a specific activity of 12.2 mCi/mg antibody, was evaluated in BALB/c mice. Radioincorporations of >90% were obtained and the radiolabeled antibody was purified by HPLC. Tissue deposition of radioactivity was evaluated in the major organs, and the skin, muscle, bone, and urine and feces over 72 hours and expressed as percent injected dose/g tissue. Results (not shown) evidenced that while the levels of radioactivity associated with the blood dropped from approximately 39.2% injected dose per gram at 1 hour to roughly 15.4% after 72 hours the levels of radioactivity associated with tail, heart, kidney, muscle and spleen remained fairly constant at 10.2% or less throughout the course of the experiment. Importantly, the radioactivity associated with the bone ranged from 4.4% of the injected dose per gram bone at 1 hour to 3.2% at 72 hours. Taken together, these results suggest that little free yttrium was associated with the conjugate and that little free radiometal was released during the course of the study. These data were used in determining radiation absorbed dose estimates for Y2B8 described below.

For tumor localization studies, 2B8-MX—DTPA was prepared and radiolabeled with ^{111}Indium to a specific activity of 2.7 mCi/mg. One hundred microliters of labeled conjugate (approximately 24 μCi) were subsequently injected into each of 12 athymic mice bearing Ramos B cell tumors. Tumors ranged in weight from 0.1 to 1.0 grams. At time points of 0, 24, 48, and 72 hours following injection, 50 μL of blood was removed by retro-orbital puncture, the mice sacrificed by cervical dislocation, and the tail, heart, lungs, liver, kidney, spleen, muscle, femur, and tumor removed. After processing and weighing the tissues, the radioactivity associated with each tissue specimen was determined using a gamma counter and the values expressed as percent injected dose per gram.

The results (not shown) evidenced that the tumor concentrations of the ^{111}In-2B8-MX—DTPA increased steadily throughout the course of the experiment. Thirteen percent of the injected dose was accumulated in the tumor after 72 hours. The blood levels, by contrast, dropped during the experiment from over 30% at time zero to 13% at 72 hours. All other tissues (except muscle) contained between 1.3 and 6.0% of the injected dose per gram tissue by the end of the experiment; muscle tissue contained approximately 13% of the injected dose per gram.

D. Human Studies

i. 2B8 and 2B8-MX—DTPA: Immunohistology Studies with Human Tissues

The tissue reactivity of murine monoclonal antibody 2B8 was evaluated using a panel of 32 different human tissues fixed with acetone. Antibody 2B8 reacts with the anti-CD20 antigen which had a very restricted pattern of tissue distribution, being observed only in a subset of cells in lymphoid tissues including those of hematopoietic origin.

In the lymph node, immunoreactivity was observed in a population of mature cortical B-lymphocytes as well as

proliferating cells in the germinal centers. Positive reactivity was also observed in the peripheral blood, B-cell areas of the tonsils, white pulp of the spleen, and with 40–70% of the medullary lymphocytes found in the thymus. Positive reactivity was also seen in the follicles of the lamina propria (Peyer's Patches) of the large intestines. Finally, aggregates or scattered lymphoid cells in the stroma of various organs, including the bladder, breast, cervix, esophagus, lung, parotid, prostate, small intestine, and stomach, were also positive with antibody 2B8 (data not shown).

All simple epithelial cells, as well as the stratified epithelia and epithelia of different organs, were found to be unreactive. Similarly, no reactivity was seen with neuroectodermal cells, including those in the brain, spinal cord and peripheral nerves. Mesenchymal elements, such as skeletal and smooth muscle cells, fibroblasts, endothelial cells, and polymorphonuclear inflammatory cells were also found to be negative (data not shown).

The tissue reactivity of the 2B8-MX—DTPA conjugate was evaluated using a panel of sixteen human tissues which had been fixed with acetone. As previously demonstrated with the native antibody (data not shown), the 2B8-MX—DTPA conjugate recognized the CD20 antigen which exhibited a highly restricted pattern of distribution, being found only on a subset of cells of lymphoid origin. In the lymph node, immunoreactivity was observed in the B cell population. Strong reactivity was seen in the white pulp of the spleen and in the medullary lymphocytes of the thymus. Immunoreactivity was also observed in scattered lymphocytes in the bladder, heart, large intestines, liver, lung, and uterus, and was attributed to the presence of inflammatory cells present in these tissues. As with the native antibody, no reactivity was observed with neuroectodermal cells or with mesenchymal elements (data not shown).

ii. Clinical Analysis of 12B8 (Imaging) and Y2B8 (Therapy)

a. Phase MI Clinical Trial Single Dose Therapy Study

A Phase I/II clinical analysis of I2B8 (imaging) followed by treatment with a single therapeutic dose of Y2B8 is currently being conducted. For the single-dose study, the following schema is being followed:

1. Peripheral Stem Cell (PSC) or Bone Marrow (BM) Harvest with Purging;
2. I2B8 Imaging;
3. Y2B8 Therapy (three Dose Levels); and
4. PSC or Autologous BM Transplantation (if necessary based upon absolute neutrophil count below 500/mm^3 for three consecutive days or platelets below 20,000/mm^3 with no evidence of marrow recovery on bone marrow examination).

The Dose Levels of Y2B8 are as follows:

Dose Level	Dose (mCi)
1.	20
2.	30
3.	40

Three patients are to be treated at each of the dose levels for determination of a Maximum Tolerated Dose ("MTD").

Imaging (Dosimetry) Studies are conducted as follows: each patient is involved in two in vivo biodistribution studies using I2B8. In the first study, 2 mg of I2B8 (5 mCi), is administered as an intravenous (i.v.) infusion over one hour; one week later 2B8 (ie, unconjugated antibody) is administered by i.v. at a rate not to exceed 250 mg/hr followed immediately by 2 mg of I2B8 (5 mCi) administered by i.v. over one hour. In both studies, immediately following the I2B8 infusion, each patient is imaged and imaging is repeated at time t=14–18 hr (if indicated), t=24 hr; t=72 hr; and t=96 hr (if indicated). Whole body average retention times for the indium [111] label are determined; such determinations are also made for recognizable organs or tumor lesions ("regions of interest").

The regions of interest are compared to the whole body concentrations of the label; based upon this comparison, an estimate of the localization and concentration of Y2B8 can be determined using standard protocols. If the estimated cumulative dose of Y2B8 is greater than eight (8) times the estimated whole body dose, or if the estimated cumulative dose for the liver exceeds 1500 cGy, no treatment with Y2B8 should occur.

If the imaging studies are acceptible, either 0.0 or 1.0 mg/kg patient body weight of 2B8 is administered by i.v. infusion at a rate not to exceed 250 mg/h. This is followed by administration of Y2B8 (10,20 or 40 mCi) at an i.v. infusion rate of 20 mCi/hr.

b. Phase I/II Clinical Trial: Multiple Dose Therapy Study

A Phase I/II clinical analysis of of Y2B8 is currently being conducted. For the multiple-dose study, the following schema is being followed:

1. PSC or BM Harvest;
2. I2B8 Imaging;
3. Y2B8 Therapy (three Dose Levels) for four doses or a total cumulative dose of 80 mCi; and
4. PSC or Autologous BM Transplantation (based upon decision of medical practitioner).

The Dose Levels of Y2B8 are as follows:

Dose Level	Dose (mCi)
1.	10
2.	15
3.	20

Three patients are to be treated at each of the dose levels for determination of an MTD.

Imaging (Dosimetry) Studies are conducted as follows: A preferred imaging dose for the unlabeled antibody (ie, 2B8) will be determined with the first two patients. The first two patients will receive 100 mg of unlabeled 2B8 in 250 cc of normal saline over 4 hrs followed by 0.5 mCi of I2B8—blood will be sampled for biodistribution data at times t=0, t=10min., t=120 min., t=24 hr, and t=48 hr. Patients will be scanned with multiple regional gamma camera images at times t=2 hr, t=24 hr and t=48 hr. After scanning at t=48 hr, the patients will receive 250 mg of 2B8 as described, followed by 4.5 mCi of I2B8 —blood and scanning will then follow as described. If 100 mg of 2B8 produces superior imaging, then the next two patients will receive 50 mg of 2B8 as described, followed by 0.5 mCi of I2B8 followed 48 hrs later by 100 mg 2B8 and then with 4.5 mCi of I2B8. If 250 mg of 2B8 produces superior imaging, then the next two patients will receive 250 mg of 2B8 as described, followed by 0.5 mCi of I2B8 followed 48 hrs later with 500 mg 2B8 and then with 4.5 mCi of I2B8. Subsequent patients will be treated with the lowest amount of 2B8 that provides optimal imaging. Optimal imaging will be defined by: (1) best effective imaging with the slowest disappearance of antibody; (2) best distribution minimizing compartmentalization in a single organ; and (3) best subjective resolution of the lesion (tumor/background comparison).

For the first four patients, the first therapeutic dose of Y2B8 will begin 14 days after the last dose of I2B8; for

subsequent patients, the first therapeutic dose of Y2B8 will begin between two to seven days after the I2B8.

Prior to treatment with Y2B8, for the patients other than the first four, 2B8 will be administered as described, followed by i.v. infusion of Y2B8 over 5–10 min. Blood will be sampled for biodistribution at times t=0, t=10min., t=120 min., t=24 hr and t=48 hr. Patients will receive repetitive doses of Y2B8 (the same dose administered as with the first dose) approximately every six to eight weeks for a maximum of four doses, or total cumulative dose of 80 mCi. It is most preferred that patients not receive a subsequent dose of Y2B8 until the patients' WBC is greater than/equal to 3,000 and AGC is greater than/equal to 100,000.

Following completion of the three-dose level study, an MTD will be defined. Additional patients will then be enrolled in the study and these will receive the MTD.

II. CHIMERIC ANTI-CD20 ANTIBODY PRODUCTION ("C2B8")

A. Construction of Chimeric Anti-CD20 Immunoglobulin DNA Expression Vector

RNA was isolated from the 2B8 mouse hybridoma cell (as described in Chomczynki, P. et al., "Single step method of RNA isolation by acid guanidinium thiocyanate-phenol-chloroform extraction." *Anal. Biochem.* 162:156–159 (1987)), and cDNA was prepared therefrom. The mouse immunoglobulin light chain variable region DNA was isolated from the cDNA by polymerase chain reaction using a set of DNA primers with homology to mouse light chain signal sequences at the 5' end and mouse light chain J region at the 3' end. Primer sequences were as follows:

1. V_L Sense SEQ. ID. NO. 8

5' ATC AC AGATCT CTC ACC ATG GAT TTT CAG GTG CAG ATT ATC AGC TTC 3'

(The underlined portion is a Bgl II site; the above-lined portion is the start codon.)

2. V_L Antisense SEQ. ID. NO. 9

5' TGC AGC ATC CGTACG TTT GAT TTC CAG CTT 3'

(The underlined portion is a Bsi WI site.)

See, FIGS. 1 and 2A–E (SEQ ID NO: 1) for the corresponding Bgl II and Bsi WI sites in TCAE 8, and FIGS. 3A–F (SEQ ID NO: 2) for the corresponding sites in anti-CD20 in TCAE 8.

These resulting DNA fragment was cloned directly into the TCAE 8 vector in front of the human kappa light chain constant domain and sequenced. The determined DNA sequence for the murine variable region light chain is set forth in FIG. 4 SEQ. ID. NO. 3–4; see also FIGS. 3A–F nucleotides **978** through **1362**. FIG. 4 further provides the amino acid sequence from this murine variable region, and the CDR and framework regions. The mouse light chain variable region from 2B8 is in the mouse kappa VI family. See, Kabat, supra.

The mouse heavy chain variable region was similarly isolated and cloned in front of the human IgG1 constant domains. Primers were as follows:

1. V_H Sense SEQ. ID. NO. 10

5' GCG GCT CCC ACGCGT GTC CTG TCC CAG 3'

(The underlined portion is an Mlu I site.)

2. V_H Antisense SEQ. ID. NO. 11

5' GG(G/C) TGT TGT GCTAGC TG(A/C) (A/G)GA GAC (G/A)GT GA 3'

(The underlined portion is an Nhe I site.)

See, FIGS. 1 and 2A–E for corresponding Mlu I and Nhe I sites in TCAE 8, and FIGS. 3A–F for corresponding sites in anti-CD20 in TCAE 8.

The sequence for this mouse heavy chain is set forth in FIG. 5 (SEQ. ID. NOS. 5–6); see also FIGS. 3A–F nucleotide **2401** through **2820**. FIG. 5 also provides the amino acid sequence from this murine variable region, and the CDR and framework regions. The mouse heavy chain variable region from 2B8 is in the mouse VH 2B family. See, Kabat, supra.

B. Creation of Chimeric Anti-CD20 Producing CHO and SP2/0 Transfectomas

Chinese hamster ovary ("CHO") cells DG44 were grown in SSFM II minus hypoxanthine and thymidine media (Gibco, Grand Island, N.Y., Form No. 91-0456PK); SP2/0 mouse myeloma cells were grown in Dulbecco's Modified Eagles Medium media ("DMEM") (Irvine Scientific, Santa Ana, Calif., Cat. No. 9024) with 5% fetal bovine serum and 20 ml/L glutamine added. Four million cells were electroporated with either 25 μg CHO or 50 μg SP2/0 plasmid DNA that had been restricted with Not I using a BTX 600 electroporation system (BTX, San Diego, Calif.) in 0.4 ml disposable cuvettes. Conditions were either 210 volts for CHO or 180 volts for SP2/0, 400 microfaradays, 13 ohms. Each electroporation was plated into six 96 well dishes (about 7,000 cells/well). Dishes were fed with media containing G418 (GENETICIN, Gibco, Cat. No. 860-1811) at 400 μg/ml active compound for CHO (media further included 50 μM hypoxanthine and 8 μM thymidine) or 800 μg/ml for SP2/0, two days following electroporation and thereafter 2 or 3 days until colonies arose. Supernatant from colonies was assayed for the presence of chimeric immunoglobulin via an ELISA specific for human antibody. Colonies producing the highest amount of immunoglobulin were expanded and plated into 96 well plates containing media plus methotrexate (25 nM for SP2/0 and 5nM for CHO) and fed every two or three days. Supernatants were assayed as above and colonies producing the highest amount of immunoglobulin were examined. Chimeric anti-CD20 antibody was purified from supernatant using protein A affinity chromatography.

Purified chimeric anti-CD20 was analyzed by electrophoresis in polyacrylamide gels and estimated to be greater than about 95% pure. Affinity and specificity of the chimeric antibody was determined based upon 2B8. Chimeric anti-CD20 antibody tested in direct and competitive binding assays, when compared to murine anti-CD20 monoclonal antibody 2B8, evidenced comparable affinity and specificity on a number of CD20 positive B cells lines (data not presented). The apparent affinity constant ("Kap") of the chimeric antibody was determined by direct binding of I^{125} radiolabeled chimeric anti-CD20 and compared to radiolabeled 2B8 by Scatchard plot; estimated Kap for CHO produced chimeric anti-CD20 was 5.2×10^{-9}M and for SP2/0 produced antibody. 7.4×10^{-9}M. The estimated Kap for 2B8 was 3.5×10^{-9}M. Direct competition by radioimmunoassay was utilized to confirm both the specificity and retention of immunoreactivity of the chimeric antibody by comparing its ability to effectively compete with 2B8. Substantially equivalent amounts of chimeric anti-CD20 and 2B8 antibodies were required to produce 50% inhibition of binding to CD20 antigens on B cells (data not presented), ie, there was a minimal loss of inhibiting activity of the anti-CD20 antibodies, presumably due to chimerization.

The results of Example II.B indicate, inter alia, that chimeric anti-CD20 antibodies were generated from CHO

and SP2/0 transfectomas using the TCAE 8 vectors, and these chimeric antibodies had substantially the same specificity and binding capability as murine anti-CD20 monoclonal antibody 2B8.

C. Determination of Immunological Activity of Chimeric Anti-CD20 Antibodies

i. Human Clq Analysis

Chimeric anti-CD20 antibodies produced by both CHO and SP2/0 cell lines were evaluated for human Clq binding in a flow cytometry assay using fluorescein labeled Clq (Clq was obtained from Quidel, Mira Mesa, Calif., Prod. No. A400 and FITC label from Sigma, St. Louis Mo., Prod. No. F-7250; FITC. Labeling of Clq was accomplished in accordance with the protocol described in *Selected Methods In Cellular Immunology*, Michell & Shiigi, Ed. (W. H. Freeman & Co., San Francisco, Calif., 1980, p. 292). Analytical results were derived using a Becton Dickinson FACScan™ flow cytometer (fluorescein measured over a range of 515–545 nm). Equivalent amounts of chimeric anti-CD20 antibody, human IgG1,K myeloma protein (Binding Site, San Diego, Calif., Prod. No. BP078), and 2B8 were incubated with an equivalent number of CD20-positive SB cells, followed by a wash step with FACS buffer (0.2% BSA in PBS, pH 7.4, 0.02% sodium azide) to remove unattached antibody, followed by incubation with FITC labeled Clq. Following a 30–60 min. incubation, cells were again washed. The three conditions, including FITC-labeled Clq as a control, were analyzed on the FACScan™ following manufacturing instructions. Results are presented in FIG. 6.

As the results of FIG. 6 evidence, a significant increase in fluorescence was observed only for the chimeric anti-CD20 antibody condition; ie, only SB cells with adherent chimeric anti-CD20 antibody were Clq positive, while the other conditions produced the same pattern as the control.

ii. Complement Dependent Cell Lyses

Chimeric anti-CD20 antibodies were analyzed for their ability to lyse lymphoma cell lines in the presence of human serum (complement source). CD20 positive SB cells were labeled with ^{51}Cr by admixing 100 μCi of ^{51}Cr with 1×10^6 SB cells for 1 hr at 37° C.; labeled SB cells were then incubated in the presence of equivalent amounts of human complement and equivalent amounts (0–50 μg/ml) of either chimeric anti-CD20 antibodies or 2B8 for 4 hrs at 37° C. (see, Brunner, K. T. et al., "Quantitative assay of the lytic action of immune lymphoid cells on ^{51}Cr-labeled allogeneic target cells in vitro." *Immunology* 14:181–189 (1968). Results are presented in FIG. 7.

The results of FIG. 7 indicate, inter alia, that chimeric anti-CD20 antibodies produced significant lysis (49%) under these conditions.

iii. Antibody Dependent Cellular Cytotoxicity Effector Assay

For this study, CD20 positive cells (SB) and CD20 negative cells (T cell leukemia line HSB; see, Adams, Richard, "Formal Discussion." Can. Res. 27:2479–2482 (1967); ATCC deposit no. ATCC CCL 120.1) were utilized; both were labeled with ^{51}Cr. Analysis was conducted following the protocol described in Brunner, K. T. et al., "Quantitative assay of the lytic action of immune lymphoid cells on ^{51}Cr-labeled allogeneic target cells in vitro; inhibition by isoantibody and drugs." Immunology 14:181–189 (1968); a substantial chimeric anti-CD20 antibody dependent cell mediated lysis of CD20 positive SB target cells (^{51}Cr-labeled) at the end of a 4 hr. 37° C. incubation, was observed and this effect was observed for both CHO and SP2/0 produced antibody (effector cells were human peripheral lymphocytes; ratio of effector cells:target was 100:1). Efficient lysis of target cells was obtained at 3.9 μg/ml. In contrast, under the same conditions, the murine anti-CD20 monoclonal antibody 2B8 had a statistically insignificant effect, and CD20 negative HSB cells were not lysed. Results are presented in FIG. 8.

The results of Example II indicate, inter alia, that the chimeric anti-CD20 antibodies of Example I were immunologically active.

III. DEPLETION OF B CELLS IN VIVO USING CHIMERIC ANTI-CD20

A. Non-Human Primate Study

Three-separate non-human primate studies were conducted. For convenience, these are referred to herein as "Chimeric Anti-CD20: CHO & SP2/0;" "Chimeric Anti-CD20: CHO;" and "High Dosage Chimeric Anti-CD20." Conditions were as follows:

Chimeric Anti-CD20: CHO & SP2/0

Six cynomolgus monkeys ranging in weight from 4.5 to 7 kilograms (White Sands Research Center, Alamogordo, N.M.) were divided into three groups of two monkeys each. Both animals of each group received the same dose of immunologically active chimeric anti-CD20 antibody. One animal in each group received purified antibody produced by the CHO transfectoma; the other received antibody produced by the SP2/0 transfectoma. The three groups received antibody dosages corresponding to 0.1 mg/kg, 0.4 mg/kg, and 1.6 mg/kg each day for four (4) consecutive days. The chimeric immunologically active anti-CD20 antibody, which was admixed with sterile saline, was administered by intravenous infusion; blood samples were drawn prior to each infusion. Additional blood samples were drawn beginning 24 hrs after the last injection (T=O) and thereafter on days 1, 3, 7, 14 and 28; blood samples were also taken thereafter at biweekly intervals until completion of the study at day 90.

Approximately 5 ml of whole blood from each animal was centrifuged at 2000 RPM for 5 min. Plasma was removed for assay of soluble chimeric anti-CD20 antibody levels. The pellet (containing peripheral blood leukocytes and red blood cells) was resuspended in fetal calf serum for fluorescent-labeled antibody analysis (see, "Fluorescent Antibody Labeling of Lymphoid Cell Population," infra.).

Chimeric Anti-CD20: CHO

Six cynomolgus monkeys ranging in weight from 4 to 6 kilograms (White Sands) were divided into three groups of two monkeys each. All animals were injected with immunologically active chimeric anti-CD20 antibodies produced from the CHO transfectoma (in sterile saline). The three groups were separated as follows: subgroup 1 received daily intravenous injections of 0.01 mg/kg of the antibody over a four (4) day period; subgroup 2 received daily intravenous injections of 0.4 mg/kg of the antibody over a four (4) day period; subgroup 3 received a single intravenous injection of 6.4 mg/kg of the antibody. For all three subgroups, a blood sample was obtained prior to initiation of treatment; additionally, blood samples were also drawn at T=0, 1, 3, 7, 14 and 28 days following the last injection, as described above, and these samples were processed for fluorescent labeled antibody analysis (see, "Fluorescent Antibody Labeling," infra.). In addition to peripheral blood B cell quantitation, lymph single cell preparation stained for quantitation of lymphocyte populations by flow cytometry.

High Dosage Chimeric Anti-CD20

Two cynomolgus monkeys (White Sands) were infused with 16.8 mg/kg of the immunologically active chimeric

anti-CD20 antibodies from the CHO transfectomas (in sterile saline) weekly over a period of four consecutive weeks. At the conclusion of the treatment, both animals were anesthetized for removal of bone marrow; lymph node biopsies were also taken. Both sets of tissue were stained for the presence of B lymphocytes using Leu 16 by flow cytometry following the protocol described in Ling, N. R. et al., "B-cell and plasma cell antigens." *Leucocyte Typing III White Cell Differentiations Antigens*, A. J. McMichael, Ed. (Oxford University Press, Oxford UK, 1987), p. 302.

Fluorescent Antibody Labeling of Lymphoid Cell Population

After removal of plasma, leukocytes were washed twice with Hanks Balanced Salt Solution ("HBSS") and resuspended in a plasma equivalent volume of fetal bovine serum (heat inactivated at 56° C. for 30 min.). A 0.1 ml volume of the cell preparation was distributed to each of six (6), 15 ml conical centrifuge tubes Fluorescein labeled monoclonal antibodies with specificity for the human lymphocyte surface markers CD2 (AMAC, Westbrook, Me.), CD20 (Becton Dickinson) and human IgM (Binding Site, San Diego, Calif.) were added to 3 of the tubes for identifying T and B lymphocyte populations. All reagents had previously tested positive to the corresponding monkey lymphocyte antigens. Chimeric anti-CD20 antibody bound to monkey B cell surface CD20 was measured in the fourth tube using polyclonal goat anti-human IgG coupled with phycoerythrin (AMAC). This reagent was pre-adsorbed on a monkey Ig-sepharose column to prevent cross-reactivity to monkey Ig, thus allowing specific detection and quantitation of chimeric anti-CD20 antibody bound to cells. A fifth tube included both anti-IgM and anti-human IgG reagents for double stained B cell population. A sixth sample was included with no reagents for determination of autofluorescence. Cells were incubated with fluorescent antibodies for 30 min., washed and fixed with 0.5 ml of fixation buffer (0.15M NaCl, 1% paraformaldehyde, pH7.4) and analyzed on a Becton Dickinson FACScan™ instrument. Lymphocyte populations were initially identified by forward versus right angle light scatter in a dot-plot bitmap with unlabeled leucocytes. The total lymphocyte population was then isolated by gating out all other events. Subsequent fluorescence measurements reflected only gated lymphocyte specific events.

Depletion of Peripheral Blood B Lymphocytes

No observable difference could be ascertained between the efficacy of CHO and SP2/0 produced antibodies in depleting B cells in vivo, although a slight increase in B cell recovery beginning after day 7 for monkeys injected with chimeric anti-CD20 antibodies derived from CHO transfectomas at dosage levels 1.6 mg/kg and 6.4 mg/kg was observed and for the monkey injected with SP2/0 producing antibody at the 0.4 mg/kg dose level. FIGS. 9A, B and C provide the results derived from the chimeric anti-CD20:CHO & SP2/0 study, with FIG. 9A directed to the 0.4 mg/kg dose level; FIG. 9B directed to the 1.6 mg/kg dose level; and FIG. 9C directed to the 6.4 mg/kg dose level.

As is evident from FIGS. 9A–C, there was a dramatic decrease (>95%) in peripheral B cell levels after the therapeutic treatment across all tested dose ranges, and these levels were maintained up to seven (7) days post infusion; after this period, B cell recovery began, and, the time of recovery initiation was independent of dosage levels.

In the Chimeric Anti-CD20:CHO study, a 10-fold lower antibody dosage concentration (0.01 mg/kg) over a period of four daily injections (0.04 mg/kg total) was utilized. FIG. 10 provides the results of this study. This dosage depleted the peripheral blood B cell population to approximately 50% of normal levels estimated with either the anti-surface IgM or the Leu 16 antibody. The results also indicate that saturation of the CD20 antigen on the B lymphocyte population was not achieved with immunologically active chimeric anti-CD20 antibody at this dose concentration over this period of time for non-human primates; B lymphocytes coated with the antibody were detected in the blood samples during the initial three days following therapeutic treatment. However, by day 7, antibody coated cells were undetectable.

Table I summarizes the results of single and multiple doses of immunologically active chimeric anti-CD20 antibody on the peripheral blood populations; single dose condition was 6.4 mg/kg; multiple dose condition was 0.4 mg/kg over four (4) consecutive days (these results were derived from the monkeys described above).

TABLE I

PERIPHERAL BLOOD POPULATION FROM C2B8 PRIMATE STUDY

Monkey	Dose	Day	CD2	Anti-Hu IgG
A	0.4 mg/kg	Prebleed	81.5	—
	(4 doses)	0	86.5	0.2
		7	85.5	0.0
		21	93.3	—
		28	85.5	—
B	0.4 mg/kg	Prebleed	81.7	—
	(4 doses)	0	94.6	0.1
		7	92.2	0.1
		21	84.9	—
		28	84.1	—
C	6.4 mg/kg	Prebleed	77.7	0.0
	(1 dose)	7	85.7	0.1
		21	86.7	—
		28	76.7	—
D	6.4 mg/kg	Prebleed	85.7	0.1
	(1 dose)	7	94.7	0.1
		21	85.2	—
		28	85.9	—

Monkey	Anti-Hu IgG + Anti-Hu IgM*	Leu-16	% B Cell Depletion
A	—	9.4	0
	0.3	0.0	97
	0.1	1.2	99
	—	2.1	78
	—	4.1	66
B	—	14.8	0
	0.2	0.1	99
	0.1	0.1	99
	—	6.9	53
	—	8.7	41
C	0.2	17.0	0
	0.1	0.0	99
	—	14.7	15
	—	8.1	62
D	0.1	14.4	0
	0.2	0.0	99
	—	9.2	46
	—	6.7	53

*Double staining population which indicates extent of chimeric anti-CD20 coated B cells.

The data summarized in Table I indicates that depletion of B cells in peripheral blood under conditions of antibody excess occurred rapidly and effectively, regardless of single or multiple dosage levels. Additionally, depletion was observed for at least seven (7) days following the last injection, with partial B cell recovery observed by day 21.

Table II summarizes the effect of immunologically active, chimeric anti-CD20 antibodies on cell populations of lymph nodes using the treatment regimen of Table I (4 daily doses

of 0.4 mg/kg; 1 dose of 6.4 mg/kg); comparative values for normal lymph nodes (control monkey, axillary and inguinal) and normal bone marrow (two monkeys) are also provided.

TABLE II

CELL POPULATIONS OF LYMPH NODES

Monkey	Dose	Day	CD2	Anti-Hu IgM
A	0.4 mg/kg	7	66.9	—
	(4 doses)	14	76.9	19.6
		28	61.6	19.7
B	0.4 mg/kg	7	59.4	—
	(4 doses)	14	83.2	9.9
		28	84.1	15.7
C	6.4 mg/kg	7	75.5	—
	(1 dose)	14	74.1	17.9
		28	66.9	23.1
D	6.4 mg/kg	7	83.8	—
	(1 dose)	14	74.1	17.9
		28	84.1	12.8

Monkey	Anti-Hu IgG + Anti-Hu IgM	Leu-16	% B Lymphocyte Depletion
A	7.4	40.1	1
	0.8	22.6	44
	—	26.0	36
B	29.9	52.2	0
	0.7	14.5	64
	—	14.6	64
C	22.3	35.2	13
	1.1	23.9	41
	—	21.4	47
D	12.5	19.7	51
	0.2	8.7	78
	—	12.9	68

	CD2	Anti-Hu IgG + Anti-Hu IgM	Anti-Hu IgM	Leu-16	% B Lymphocyte Depletion
Normal Lymph Nodes Control 1					
Axillary	55.4	25.0	—	41.4	NA
Inguinal	52.1	31.2	—	39.5	NA
Normal Bone Marrow					
Control 2	65.3	19.0	—	11.4	NA
Control 3	29.8	28.0	—	16.6	NA

The results of Table II evidence effective depletion of B lymphocytes for both treatment regimens. Table II further indicates that for the non-human primates, complete saturation of the B cells in the lymphatic tissue with immunologically active, chimeric anti-CD20 antibody was not achieved; additionally, antibody coated cells were observed seven (7) days after treatment, followed by a marked depletion of lymph node B cells, observed on day 14.

Based upon this data, the single High Dosage Chimeric Anti-CD20 study referenced above was conducted, principally with an eye toward pharmacology/toxicology determination. Ie this study was conducted to evaluate any toxicity associated with the administration of the chimeric antibody, as well as the efficacy of B cell depletion from peripheral blood lymph nodes and bone marrow. Additionally, because the data of Table II indicates that for that study, the majority of lymph node B cells were depleted between 7 and 14 days following treatment, a weekly dosing regimen might evidence more efficacious results. Table III summarizes the results of the High Dosage Chimeric Anti-CD20 study.

TABLE III

CELL POPULATIONS OF LYMPH NODES AND BONE MARROW

	Lymphocyte Populations (%)				
Monkey	CD2	CD20[a]	mIgM + anti-C2B8[b]	C2B8[c]	Day[d]
		Inguinal Lymph Node			
E	90.0	5.3	4.8	6.5	22
F	91.0	6.3	5.6	6.3	22
G	89.9	5.0	3.7	5.8	36
H	85.4	12.3	1.7	1.8	36
		Bone Marrow			
E	46.7	4.3	2.6	2.8	22
F	41.8	3.0	2.1	2.2	22
G	35.3	0.8	1.4	1.4	36
H	25.6	4.4	4.3	4.4	36

[a]Indicates population stained with Leu 16.
[b]Indicates double staining population, positive for surface IgM cells and chimeric antibody coated cells.
[c]Indicates total population staining for chimeric antibody including double staining surface IgM positive cells and single staining (surface IgM negative) cells.
[d]Days after injection of final 16.8 mg/kg dose.

Both animals evaluated at 22 days post treatment cessation contained less than 5% B cells, as compared to 40% in control lymph nodes (see, Table II, supra). Similarly, in the bone marrow of animals treated with chimeric anti-CD20 antibody, the levels of CD20 positive cells were less than 3% as compared to 11–15% in the normal animals (see, Table II, supra). In the animals evaluated at 36 days post treatment cessation, one of the animals (H) had approximately 12% B cells in the lymph node and 4.4% B cells in bone marrow, while the other (G) had approximately 5% B cells in the lymph node and 0.8% in the bone marrow—the data is indicative of significant B cell depletion.

The results of Example IIIA indicate, inter alia, that low doses of immunologically active, chimeric anti-CD20 leads to long-term peripheral blood B cell depletion in primates. The data also indicates that significant depletion of B cell populations was achieved in peripheral lymph nodes and bone marrow when repetitive high doses of the antibody were administered. Continued follow-up on the test animals has indicated that even with such severe depletion of peripheral B lymphocytes during the first week of treatment, no adverse health effects have been observed. Furthermore, as recovery of B cell population was observed, a conclusion to be drawn is that the pluripotent stem cells of these primates were not adversely affected by the treatment.

B. Clinical Analysis of C2B8

i. Phase I/II Clinical Trial of C2B8: Single Dose Therapy Study

Fifteen patients having histologically documented relapsed B cell lymphoma have been treated with C2B8 in a Phase I/II Clinical Trial. Each patient received a single dose of C2B8 in a dose-escalating study; there were three patients per dose: 10 mg/m^2; 50 mg/m^2; 100 mg/m^2; 250 mg/m^2 and 500 mg/m^2. Treatment was by i.v. infusion through an 0.22 micron in-line filter with C2B8 being diluted in a final volume of 250 cc or a maximal concentration of 1 mg/ml of normal saline. Initial rate was 50 cc/hr for the first hour; if no toxicity was seen, dose rate was able to be escalated to a maximum of 200 cc/hr.

Toxicity (as indicated by the clinician) ranged from "none", to "fever" to "moderate" (two patients) to "severe" (one patient); all patients completed the therapy treatment. Peripheral Blood Lymphocytes were analyzed to determine, inter alia, the impact of C2B8 on T-cells and B-cells.

Consistently for all patients, Peripheral Blood B Lymphocytes were depleted after infusion with C2B8 and such depletion was maintained for in excess of two weeks.

One patient (receiving 100 mg/^{2} of C2B8) evidenced a Partial Response to the C2B8 treatment (reduction of greater than 50% in the sum of the products of the perpendicular diameters of all measurable indicator lesions lasting greater than four weeks, during which no new lesions may appear and no existing lesions may enlarge); at least one other patient (receiving 500 mg/m^2) evidenced a Minor Response to the C2B8 treatment (reduction of less than 50% but at least 25% in the sum of the products of the two longest perpendicular diameters of all measurable indicator lesions). For presentational efficiency, results of the PBLs are set forth in FIGS. 14A and B; data for the patient evidencing a PR is set forth in FIG. 14A; for the patient evidencing an MR, data is set forth in FIG. 14B. In FIGS. 14 and B, the following are applicable:

■ = Lymphocytes; ⊖ = CD3+ cells (T cells);

▲ = CD20$^+$ cells; ● = CD19$^+$ cells; ⊖ = Kappa; -▲- = lambda; and -●- = C2B8.

As evidenced, the B cell markers CD20 and CD19, Kappa and Lambda, were depleted for a period in excess of two weeks; while there was a slight, initial reduction in T-cell counts, these returned to an approximate base-line level in a relatively rapid time-frame.

ii. Phase I/II Clinical Trial of C2B8: Multiple Dose Therapy Study

Patients having histologically confirmed B cell lymphoma with measurable progressive disease are eligible for this study which is separated into two parts: in Phase I, consisting of a dose escalation to characterize dose limiting toxicities and determination of biologically active tolerated dose level, groups of three patients will receive weekly i.v. infusions of C2B8 for a total of four (4) separate infusions. Cumulative dose at each of the three levels will be as follows: 500 mg/m^2 (125 mg/m^2/infusion); 1000 mg/m^2 (250 mg/m^2/infusion); 1500 mg/m^2 (375 mg/m^2/infusion. A biologically active tolerated dose is defined, and will be determined, as the lowest dose with both tolerable toxicity and adequate activity); in Phase II, additional patients will receive the biologically active tolerated dose with an emphasis on determining the activity of the four doses of C2B8.

IV. COMBINATION THERAPY: C2B8 AND Y2B8

A combination therapeutic approach using C2B8 and Y2B8 was investigated in a mouse xenographic model (nu/nu mice, female, approximately 10 weeks old) utilizing a B cell lymphoblastic tumor (Ramos tumor cells). For comparative purposes, additional mice were also treated with C2B8 and Y2B8.

Ramos tumor cells (ATCC, CRL 1596) were maintained in culture using RPMI-1640 supplemented with 10% fetal calf serum and glutamine at 37° C. and 5% CO_2. Tumors were initiated in nine female nude mice approximately 7–10 weeks old by subcutaneous injection of 1.7×10^6 Ramos cells in a volume of 0.10 ml (HBSS) using a 1 cc syringe fitted with 25 g needle. All animals were manipulated in a laminar flow hood and all cages, bedding, food and water were autoclaved. Tumor cells were passaged by excising tumors and passing these through a 40 mesh screen; cells were washed twice with 1X HBSS (50 ml) by centrifugation (1300 RPM), resuspended in 1X HBSS to 10×10^6 cells/ml, and frozen at −70° C. until used.

For the experimental conditions, cells from several frozen lots were thawed, pelleted by centrifugation (1300 RPM) and washed twice with 1X HBSS. Cells were then resuspended to approximately 2.0×10^6 cells/ml. Approximately 9 to 12 mice were injected with 0.10 ml of the cell suspension (s.c.) using a 1 cc syringe fitted with a 25 g needle; injections were made on the animal's left side, approximately mid-region. Tumors developed in approximately two weeks. Tumors were excised and processed as described above. Study mice were injected as described above with 1.67×10^6 cells in 0.10 ml HBSS.

Based on preliminary dosing experiments, it was determined that 200 mg of C2B8 and 100 μCi of Y2B8 would be utilized for the study. Ninety female nu/nu mice (approximately 10 weeks old) were injected with the tumor cells. Approximately ten days later, 24 mice were assigned to four study groups (six mice/group) while attempting to maintain a comparable tumor size distribution in each group (average tumor size, expressed as a product of length×width of the tumor, was approximately 80 mm^2). The following groups were treated as indicated via tail-vain injections using a 100 μl Hamilton syringe fitted with a 25 g needle:

A. Normal Saline

B. Y2B8 (100 Ci)

C. C2B8 (200 μg); and

D. Y2B8 (100 Ci) +C2B8 (200μg)

Groups tested with C2B8 were given a second C2B8 injection (200 μg/mouse) seven days after the initial injection. Tumor measurements were made every two or three days using a caliper.

Preparation of treatment materials were in accordance with the following protocols:

A. Preparation of Y2B8

Yttrium-[90] chloride (6 mCi) was transformed to a polypropylene tube and adjusted to pH 4.1–4.4 using metal free 2M sodium acetate. 2B8-MX—DTPA (0.3 mg in normal saline; see above for preparation of 2B8-MX—DTPA) was added and gently mixed by vortexing. After 15 min. incubation, the reaction was quenched by adding 0.05× volume 20 mM EDTA and 0.05×volume 2M sodium acetate. Radioactivity concentration was determined by diluting 5.0 μl of the reaction mixture in 2.5 ml×PBS containing 75 mg/ml HSA and 1 mM DTPA ("formulation buffer"); counting was accomplished by adding 10.0I to 20 ml of Ecolume™ scintillation cocktail. The remainder of the reactive mixture was added to 3.0 ml formulation buffer, sterile filtered and stored at 2°–8° C. until used. Specific activity (14 mCi/mg at time of injection) was calculated using the radioactivity concentration and the calculated protein concentration based upon the amount of antibody added to the reaction mixture. Protein-associated radioactivity was determined using instant thin-layer chromatography. Radioincorporation was 95%. Y2B8 was diluted in formulation buffer immediately before use and sterile-filtered (final radioactivity concentration was 1.0 mCi/ml).

B. Preparation of C2B8

C2B8 was prepared as described above. C2B8 was provided as a sterile reagent in normal saline at 5.0 mg/ml. Prior to injection, the C2B8 was diluted in normal saline to 2.0 mg/ml and sterile filtered.

C. Results

Following treatment, tumor size was expressed as a product of length and width, and measurements were taken on the days indicated in FIG. 11 (Y2B8 vs. Saline); FIG. 12 (C2B8 vs. Saline); and FIG. 13 (Y2B8+C2B8 vs. Saline). Standard error was also determined.

As indicated in FIG. 13, the combination of Y2B8 and C2B8 exhibited tumoricidal effects comparable to the effects evidenced by either Y2B8 or C2B8.

V. ALTERNATIVE THERAPY STRATEGIES

Alternative therapeutic strategies recognized in view of the foregoing examples are evident. One such strategy employs the use of a therapeutic dose of C2B8 followed within about one week with a combination of either 2B8 and radiolabeled 2B8 (eg, Y2B8); or 2B8, C2B8 and, eg, Y2B8; or C2B8 and, eg, Y2B8. An additional strategy is utilization of radiolabeled C2B8—such a strategy allows for utilization of the benefits of the immunologically active portion of C2B8 plus those benefits associated with a radiolabel. Preferred radiolabels include yttrium-90 given the larger circulating half-life of C2B8 versus the murine antibody 2B8. Because of the ability of C2B8 to deplete B-cells, and the benefits to be derived from the use of a radiolabel, a preferred alternative strategy is to treat the patient with C2B8 (either with a single dose or multiple doses) such that most, if not all, peripheral B cells have been depleted. This would then be followed with the use of radiolabeled 2B8; because of the depletion of peripheral B cells, the radiolabeled 2B8 stands an increased chance of targeting tumor cells. Iodine [131] labeled 2B8 is preferably utilized, given the types of results reported in the literature with this label (see Kaminski). An alternative preference involves the use of a radiolabeled 2B8 (or C2B8) first in an effort to increase the permeability of a tumor, followed by single or multiple treatments with C2B8; the intent of this strategy is to increase the chances of the C2B8 in getting both outside and inside the tumor mass. A further strategy involved the use of chemotherapeutic agenst in combination with C2B8. These strategies include so-called "staggered" treatments, ie, treatment with chemotherapeutic agent, followed by treatment with C2B8, followed by a repetition of this protocol. Alternatively, initial treatment with a single or multiple doses of C2B8, thereafter followed with chemotherapeutic treatement, is viable. Preferred chemotherapeutic agents include, but are not limited to: cyclophlsphamide; doxorubicin; vincristine; and prednisone. See Armitage, J. O. et al., *Cancer* 50:1695 (1982), incorporated herein by reference.

The foregoing alternative therapy strategies are not intended to be limiting, but rather are presented as being representative.

VI. DEPOSIT INFORMATION

Anti-CD20 in TCAE 8 (transformed in *E. coli* for purposes of deposit) was deposited with the American Type Culture Collection (ATCC) on Nov. 4, 1992, 12301 Parklawn Drive, Rockville, Md., 20852, under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure ("Budapest Treaty"). The microorganism was tested by the ATCC on Nov. 9, 1992, and determined to be viable on that date. The ATCC has assigned this microorganism for the following ATCC deposit number: ATCC 69119 (anti-CD20 in TCAE 8). Hybridoma 2B8 was deposited with the ATCC on Jun. 22, 1993 under the provisions of the Budapest Treaty. The viability of the culture was determined on Jun. 25, 1993 and the ATCC has assigned this hybridoma the following ATCC deposit number: HB 11388.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i i i) NUMBER OF SEQUENCES: 11

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8541 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i i i) POSITION IN GENOME:
(A) CHROMOSOME/SEGMENT: TCAE 8

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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GCTGCTATTG GGCGAAGTGC CGGGGCAGGA TCTCCTGTCA TCTCACCTTG CTCCTGCCGA   5580
GAAAGTATCC ATCATGGCTG ATGCAATGCG GCGGCTGCAT ACGCTTGATC CGGCTACCTG   5640
CCCATTCGAC CACCAAGCGA AACATCGCAT CGAGCGAGCA CGTACTCGGA TGGAAGCCGG   5700
TCTTGTCGAT CAGGATGATC TGGACGAAGA GCATCAGGGG CTCGCGCCAG CCGAACTGTT   5760
CGCCAGGCTC AAGGCGCGCA TGCCCGACGG CGAGGATCTC GTCGTGACCC ATGGCGATGC   5820
CTGCTTGCCG AATATCATGG TGGAAAATGG CCGCTTTTCT GGATTCATCG ACTGTGGCCG   5880
GCTGGGTGTG GCGGACCGCT ATCAGGACAT AGCGTTGGCT ACCCGTGATA TTGCTGAAGA   5940
GCTTGGCGGC GAATGGGCTG ACCGCTTCCT CGTGCTTTAC GGTATCGCCG CTTCCCGATT   6000
CGCAGCGCAT CGCCTTCTAT CGCCTTCTTG ACGAGTTCTT CTGAGCGGGA CTCTGGGGTT   6060
CGAAATGACC GACCAAGCGA CGCCCAACCT GCCATCACGA GATTTCGATT CCACCGCCGC   6120
CTTCTATGAA AGGTTGGGCT TCGGAATCGT TTTCCGGGAC GCCGGCTGGA TGATCCTCCA   6180
GCGCGGGGAT CTCATGCTGG AGTTCTTCGC CCACCCCAAC TTGTTTATTG CAGCTTATAA   6240
TGGTTACAAA TAAAGCAATA GCATCACAAA TTTCACAAAT AAAGCATTTT TTTCACTGCA   6300
TTCTAGTTGT GGTTTGTCCA AACTCATCAA TCTATCTTAT CATGTCTGGA TCGCGGCCGC   6360
GATCCCGTCG AGAGCTTGGC GTAATCATGG TCATAGCTGT TTCCTGTGTG AAATTGTTAT   6420
CCGCTCACAA TTCCACACAA CATACGAGCC GGAAGCATAA AGTGTAAAGC CTGGGGTGCC   6480
TAATGAGTGA GCTAACTCAC ATTAATTGCG TTGCGCTCAC TGCCCGCTTT CCAGTCGGGA   6540
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ATTGGGCGCT CTTCCGCTTC CTCGCTCACT GACTCGCTGC GCTCGGTCGT TCGGCTGCGG   6660
CGAGCGGTAT CAGCTCACTC AAAGGCGGTA ATACGGTTAT CCACAGAATC AGGGGATAAC   6720
GCAGGAAAGA ACATGTGAGC AAAAGGCCAG CAAAAGGCCA GGAACCGTAA AAAGGCCGCG   6780
TTGCTGGCGT TTTTCCATAG GCTCCGCCCC CCTGACGAGC ATCACAAAAA TCGACGCTCA   6840
AGTCAGAGGT GGCGAAACCC GACAGGACTA TAAAGATACC AGGCGTTTCC CCCTGGAAGC   6900
TCCCTCGTGC GCTCTCCTGT TCCGACCCTG CCGCTTACCG GATACCTGTC CGCCTTTCTC   6960
CCTTCGGGAA GCGTGGCGCT TTCTCAATGC TCACGCTGTA GGTATCTCAG TTCGGTGTAG   7020
GTCGTTCGCT CCAAGCTGGG CTGTGTGCAC GAACCCCCCG TTCAGCCCGA CCGCTGCGCC   7080
TTATCCGGTA ACTATCGTCT TGAGTCCAAC CCGGTAAGAC ACGACTTATC GCCACTGGCA   7140
GCAGCCACTG GTAACAGGAT TAGCAGAGCG AGGTATGTAG GCGGTGCTAC AGAGTTCTTG   7200
AAGTGGTGGC CTAACTACGG CTACACTAGA AGGACAGTAT TTGGTATCTG CGCTCTGCTG   7260
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GAAGATCCTT TGATCTTTTC TACGGGGTCT GACGCTCAGT GGAACGAAAA CTCACGTTAA   7440
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TGAAGTTTTA AATCAATCTA AAGTATATAT GAGTAAACTT GGTCTGACAG TTACCAATGC   7560
TTAATCAGTG AGGCACCTAT CTCAGCGATC TGTCTATTTC GTTCATCCAT AGTTGCCTGA   7620
CTCCCCGTCG TGTAGATAAC TACGATACGG GAGGGCTTAC CATCTGGCCC CAGTGCTGCA   7680
ATGATACCGC GAGACCCACG CTCACCGGCT CCAGATTTAT CAGCAATAAA CCAGCCAGCC   7740
GGAAGGGCCG AGCGCAGAAG TGGTCCTGCA ACTTTATCCG CCTCCATCCA GTCTATTAAT   7800
TGTTGCCGGG AAGCTAGAGT AAGTAGTTCG CCAGTTAATA GTTTGCGCAA CGTTGTTGCC   7860
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TCCCAACGAT CAAGGCGAGT TACATGATCC CCCATGTTGT GCAAAAAAGC GGTTAGCTCC   7980
TTCGGTCCTC CGATCGTTGT CAGAAGTAAG TTGGCCGCAG TGTTATCACT CATGGTTATG   8040
GCAGCACTGC ATAATTCTCT TACTGTCATG CCATCCGTAA GATGCTTTTC TGTGCATGGT   8100
GAGTACTCAA CCAAGTCATT CTGAGAATAG TGTATGCGGC GACCGAGTTG CTCTTGCCCG   8160
GCGTCAATAC GGGATAATAC CGCGCCACAT AGCAGAACTT TAAAAGTGCT CATCATTGGA   8220
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TAACCCACTC GTGCACCCAA CTGATCTTCA GCATCTTTTA CTTTCACCAG CGTTTCTGGG   8340
TGAGCAAAAA CAGGAAGGCA AAATGCCGCA AAAAAGGGAA TAAGGGCGAC ACGGAAATGT   8400
TGAATACTCA TACTCTTCCT TTTTCAATAT TATTGAAGCA TTTATCAGGG TTATTGTCTC   8460
ATGAGCGGAT ACATATTTGA ATGTATTTAG AAAAATAAAC AAATAGGGGT TCCGCGCACA   8520
TTTCCCCGAA AAGTGCCACC T                                             8541
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(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9209 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i i i) POSITION IN GENOME:
(A) CHROMOSOME/SEGMENT: anti-CD20 in TCAE 8

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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GACGTCGCGG CCGCTCTAGG CCTCCAAAAA AGCCTCCTCA CTACTTCTGG AATAGCTCAG     60
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GGAGAATGGG CGGAACTGGG CGGAGTTAGG GGCGGGATGG GCGGAGTTAG GGGCGGGACT    180
ATGGTTGCTG ACTAATTGAG ATGCATGCTT TGCATACTTC TGCCTGCTGG GGAGCCTGGG    240
GACTTTCCAC ACCTGGTTGC TGACTAATTG AGATGCATGC TTTGCATACT TCTGCCTGCT    300
GGGGAGCCTG GGGACTTTCC ACACCCTAAC TGACACACAT TCCACAGAAT TAATTCCCCT    360
AGTTATTAAT AGTAATCAAT TACGGGGTCA TTAGTTCATA GCCCATATAT GGAGTTCCGC    420
GTTACATAAC TTACGGTAAA TGGCCCGCCT GGCTGACCGC CCAACGACCC CCGCCCATTG    480
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ACGTCAATAA TGACGTATGT TCCCATAGTA ACGCCAATAG GGACTTTCCA TTGACGTCAA   540
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AGTACGCCCC CTATTGACGT CAATGACGGT AAATGGCCCG CCTGGCATTA TGCCCAGTAC   660
ATGACCTTAT GGGACTTTCC TACTTGGCAG TACATCTACG TATTAGTCAT CGCTATTACC   720
ATGGTGATGC GGTTTTGGCA GTACATCAAT GGGCGTGGAT AGCGGTTTGA CTCACGGGGA   780
TTTCCAAGTC TCCACCCCAT TGACGTCAAT GGGAGTTTGT TTTGGCACCA AAATCAACGG   840
GACTTTCCAA AATGTCGTAA CAACTCCGCC CCATTGACGC AAATGGGCGG TAGGCGTGTA   900
CGGTGGGAGG TCTATATAAG CAGAGCTGGG TACGTGAACC GTCAGATCGC CTGGAGACGC   960
CATCACAGAT CTCTCACTAT GGATTTTCAG GTGCAGATTA TCAGCTTCCT GCTAATCAGT  1020
GCTTCAGTCA TAATGTCCAG AGGACAAATT GTTCTCTCCC AGTCTCCAGC AATCCTGTCT  1080
GCATCTCCAG GGGAGAAGGT CACAATGACT TGCAGGGCCA GCTGAAGTGT AAGTTACATC  1140
CACTGGTTCC AGCAGAAGCC AGGATCCTCC CCCAAACCCT GGATTTATGC CACATCCAAC  1200
CTGGCTTCTG GAGTCCCTGT TCGCTTCAGT GGCAGTGGGT CTGGGACTTC TTACTCTCTC  1260
ACCATCAGCA GAGTGGAGGC TGAAGATGCT GCCACTTATT ACTGCCAGCA GTGGACTAGT  1320
AACCCACCCA CGTTCGGAGG GGGGACCAAG CTGGAAATCA AACGTACGGT GGCTGCACCA  1380
TCTGTCTTCA TCTTCCCGCC ATCTGATGAG CAGTTGAAAT CTGGAACTGC CTCTGTTGTG  1440
TGCCTGCTGA ATAACTTCTA TCCCAGAGAG GCCAAAGTAC AGTGGAAGGT GGATAACGCC  1500
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AGCCTCAGCA GCACCCTGAC GCTGAGCAAA GCAGACTACG AGAAACACAA AGTCTACGCC  1620
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GGCCGTGATA TCTACGTATG ATCAGCCTCG ACTGTGCCTT CTAGTTGCCA GCCATCTGTT  1800
GTTTGCCCCT CCCCCGTGCC TTCCTTGACC CTGGAAGGTG CCACTCCCAC TGTCCTTTCC  1860
TAATAAAATG AGGAAATTGC ATCGCATTGT CTGAGTAGGT GTCATTCTAT TCTGGGGGGT  1920
GGGGTGGGGC AGGACAGCAA GGGGGAGGAT TGGGAAGACA ATAGCAGGCA TGCTGGGGAT  1980
GCGGTGGGCT CTATGGAACC AGCTGGGGCT CGACAGCTAT GCCAAGTACG CCCCCTATTG  2040
ACGTCAATGA CGGTAAATGG CCCGCCTGGC ATTATGCCCA GTACATGACC TTATGGGACT  2100
TTCCTACTTG GCAGTACATC TACGTATTAG TCATCGCTAT TACCATGGTG ATGCGGTTTT  2160
GGCAGTACAT CAATGGGCGT GGATAGCGGT TTGACTCACG GGGATTTCCA AGTCTCCACC  2220
CCATTGACGT CAATGGGAGT TTGTTTTGGC ACCAAAATCA ACGGGACTTT CCAAAATGTC  2280
GTAACAACTC CGCCCCATTG ACGCAAATGG GCGGTAGGCG TGTACGGTGG GAGGTCTATA  2340
TAAGCAGAGC TGGGTACGTC CTCACATTCA GTGATCAGCA CTGAACACAG ACCCGTCGAC  2400
ATGGGTTGGA GCCTCATCTT GCTCTTCCTT GTCGCTGTTG CTACGCGTGT CCTGTCCCAG  2460
GTACAACTGC AGCAGCCTGG GGCTGAGCTG GTGAAGCCTG GGGCCTCAGT GAAGATGTCC  2520
TGCAAGGCTT CTGGCTACAC ATTTACCAGT TACAATATGC ACTGGGTAAA ACAGACACCT  2580
GGTCGGGGCC TGGAATGGAT TGGAGCTATT TATCCCGGAA ATGGTGATAC TTCCTACAAT  2640
CAGAAGTTCA AAGGCAAGGC CACATTGACT GCAGACAAAT CCTCCAGCAC AGCCTACATG  2700
CAGCTCAGCA GCCTGACATC TGAGGACTCT GCGGTCTATT ACTGTGCAAG ATCGACTTAC  2760
TACGGCGGTG ACTGGTACTT CAATGTCTGG GGCGCAGGGA CCACGGTCAC CGTCTCTGCA  2820
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AAATCTTGTG ACAAAACTCA CACATGCCCA CCGTGCCCAG CACCTGAACT CCTGGGGGGA   3180
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GAGGTCACAT GCGTGGTGGT GGACGTGAGC CACGAAGACC CTGAGGTCAA GTTCAACTGG   3300
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GAGTACAAGT GCAAGGTCTC CAACAAAGCC CTCCCAGCCC CCATCGAGAA AACCATCTCC   3480
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TTGGGAAGAC AATAGCAGGC ATGCTGGGGA TGCGGTGGGC TCTATGGAAC CAGCTGGGGC   5520
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ATTGTCTCAT GAGCGGATAC ATATTTGAAT GTATTTAGAA AAATAAACAA ATAGGGGTTC   9180
CGCGCACATT TCCCCGAAAA GTGCCACCT                                     9209
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(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 384 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: Not Relevant
(D) TOPOLOGY: Not Relevant

(i i) MOLECULE TYPE: peptide

(v i i i) POSITION IN GENOME:
(A) CHROMOSOME/SEGMENT: murine variable region light chain

(i x) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..384

(i x) FEATURE:
(A) NAME/KEY: mat_peptide
(B) LOCATION: 67..384

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:3:

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-22      -20                 -15                 -10
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GTC ATA ATG TCC AGA GGA CAA ATT GTT CTC TCC CAG TCT CCA GCA ATC          96
Val Ile Met Ser Arg Gly Gln Ile Val Leu Ser Gln Ser Pro Ala Ile
 -5                          1                   5                  10

CTG TCT GCA TCT CCA GGG GAG AAG GTC ACA ATG ACT TGC AGG GCC AGC         144
Leu Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr Cys Arg Ala Ser
                15                  20                  25

TCA AGT GTA AGT TAC ATC CAC TGG TTC CAG CAG AAG CCA GGA TCC TCC         192
Ser Ser Val Ser Tyr Ile His Trp Phe Gln Gln Lys Pro Gly Ser Ser
            30                  35                  40

CCC AAA CCC TGG ATT TAT GCC ACA TCC AAC CTG GCT TCT GGA GTC CCT         240
Pro Lys Pro Trp Ile Tyr Ala Thr Ser Asn Leu Ala Ser Gly Val Pro
        45                  50                  55

GTT CGC TTC AGT GGC AGT GGG TCT GGG ACT TCT TAC TCT CTC ACC ATC         288
Val Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile
    60                  65                  70

AGC AGA GTG GAG GCT GAA GAT GCT GCC ACT TAT TAC TGC CAG CAG TGG         336
Ser Arg Val Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp
75                  80                  85                  90

ACT AGT AAC CCA CCC ACG TTC GGA GGG GGG ACC AAG CTG GAA ATC AAA         384
Thr Ser Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
                95                 100                 105
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(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 128 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: protein

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:4:

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-22          -20                 -15                 -10

Val Ile Met Ser Arg Gly Gln Ile Val Leu Ser Gln Ser Pro Ala Ile
 -5                          1                   5                  10

Leu Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr Cys Arg Ala Ser
                15                  20                  25

Ser Ser Val Ser Tyr Ile His Trp Phe Gln Gln Lys Pro Gly Ser Ser
            30                  35                  40

Pro Lys Pro Trp Ile Tyr Ala Thr Ser Asn Leu Ala Ser Gly Val Pro
        45                  50                  55

Val Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile
    60                  65                  70

Ser Arg Val Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp
75                  80                  85                  90

Thr Ser Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
                95                 100                 105
```

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 420 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: Not Relevant
(D) TOPOLOGY: Not Relevant

(i i) MOLECULE TYPE: peptide

(v i i i) POSITION IN GENOME:
(A) CHROMOSOME/SEGMENT: murine variable region heavy chain

(i x) FEATURE:

-continued

(A) NAME/KEY: CDS
(B) LOCATION: 1..420

(i x) FEATURE:
(A) NAME/KEY: mat_peptide
(B) LOCATION: 58..420

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:5:

```
ATG GGT TGG AGC CTC ATC TTG CTC TTC CTT GTC GCT GTT GCT ACG CGT        48
Met Gly Trp Ser Leu Ile Leu Leu Phe Leu Val Ala Val Ala Thr Arg
-19                 -15                 -10                 -5

GTC CTG TCC CAG GTA CAA CTG CAG CAG CCT GGG GCT GAG CTG GTG AAG        96
Val Leu Ser Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys
                 1               5                  10

GCT GGG GCC TCA GTG AAG ATG TCC TGC AAG GCT TCT GGC TAC ACA TTT       144
Ala Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe
     15                  20                  25

ACC AGT TAC AAT ATG CAC TGG GTA AAA CAG ACA CCT GGT CGG GGC CTG       192
Thr Ser Tyr Asn Met His Trp Val Lys Gln Thr Pro Gly Arg Gly Leu
 30                  35                  40                  45

GAA TGG ATT GGA GCT ATT TAT CCC GGA AAT GGT GAT ACT TCC TAC AAT       240
Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn
                 50                  55                  60

CAG AAG TTC AAA GGC AAG GCC ACA TTG ACT GCA GAC AAA TCC TCC AGC       288
Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser
             65                  70                  75

ACA GCC TAC ATG CAG CTC AGC AGC CTG ACA TCT GAG GAC TCT GCG GTC       336
Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
         80                  85                  90

TAT TAC TGT GCA AGA TCG ACT TAC TAC GGC GGT GAC TGG TAC TTC AAT       384
Tyr Tyr Cys Ala Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn
     95                 100                 105

GTC TGG GGC GCA GGG ACC ACG GTC ACC GTC TCT GCA                       420
Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ala
110                 115                 120
```

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 140 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: protein

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:6:

```
Met Gly Trp Ser Leu Ile Leu Leu Phe Leu Val Ala Val Ala Thr Arg
-19                 -15                 -10                 -5

Val Leu Ser Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys
                 1               5                  10

Ala Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe
     15                  20                  25

Thr Ser Tyr Asn Met His Trp Val Lys Gln Thr Pro Gly Arg Gly Leu
 30                  35                  40                  45

Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn
                 50                  55                  60

Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser
             65                  70                  75

Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
         80                  85                  90

Tyr Tyr Cys Ala Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn
     95                 100                 105
```

-continued

Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ala
110 115 120

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GGGAGCTTGG ATCGATCCTC TATGGTT 27

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i v) ANTI-SENSE: NO

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:8:

ATCACAGATC TCTCACCATG GATTTTCAGG TGCAGATTAT CAGCTTC 47

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i v) ANTI-SENSE: YES

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:9:

TGCAGCATCC GTACGTTTGA TTTCCAGCTT 30

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i v) ANTI-SENSE: NO

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:10:

GCGGCTCCCA CGCGTGTCCT GTCCCAG 27

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

-continued

(i v) ANTI-SENSE: YES

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GGSTGTTGTG CTAGCTGMRG AGACRGTGA 29

What is claimed is:

1. A method for treatment of B cell lymphoma comprising the step of administering a therapeutically effective amount of immunologically active chimeric anti-CD20 antibody to a human, said antibody being derived from a transfectoma comprising anti-CD20 in TCAE 8, ATCC deposit number 69119.

2. The method of claim 1 wherein the amount of said antibody administered to said human is between about 0.001 to about 30 milligrams of antibody per kilogram body weight of said human ("mg/kg").

3. The method of claim 1 further comprising the step of administering a second therapeutically effective amount of said chimeric anti-CD20 antibody to said human.

4. The method of claim 3 wherein said additional administration of said antibody to said human occurs within about seven days of said first administration of said antibody to said human.

5. A method for the treatment of B cell lymphoma comprising the steps of:

1) administering, at a first administration period, an immunologically active chimeric anti-CD20 antibody to a human, wherein said chimeric anti-CD20 antibody is derived from a transfectoma comprising anti-CD20 in TCAE 8 as deposited with the American Type Culture Collection as ATCC deposit number 69119; and,

2) administering, at a second administration period, a radiolabeled anti-CD20 antibody to said human.

6. The method of claim 5 wherein said radiolabeled anti-CD20 antibody comprises a monoclonal antibody secreted from a hybridoma identified by American Type Culture Collection deposit number HB 11388.

7. A method for the treatment of B cell lymphoma comprising the steps of:

1) administering to a human having B cell lymphoma, at a first administration period, a first therapeutically effective amount of immunologically active chimeric anti-CD20 antibody produced by a transfectoma comprising anti-CD20 in TCAE8, ATCC deposit number 69119;

2) administering at a second subsequent administration period, a second therapeutically effective amount of said antibody; and

3) administering, at a third subsequent administration period, a third therapeutically effective amount of said antibody.

8. The method of claim 7, wherein said first, second and third therapeutically effective amount of said antibody is between 0.001 mg/kg to about 30 mg/kg.

9. The method of claim 7, wherein said second administration period is within about seven days of said first administration period.

10. The method of claim 7, wherein said third administration period is within about fourteen days of said first administration period.

11. The method of claim 1, which further includes the administration of at least one chemotherapeutic agent.

12. The method of claim 11, wherein the chemotherapeutic agent is administered after the administration of said immunologically active chimeric anti-CD20 antibody.

13. The method of claim 11, wherein the chemotherapeutic agent is administered prior to the administration of said immunologically active chimeric anti-CD20 antibody.

14. The method of claim 11, wherein the chemotherapeutic agents are selected from the group consisting of cyclophosphamide doxorubicin, vincristine and prednisone.

* * * * *

Exhibit C

Maintenance Fee Statement
for U.S. Patent 5,776,456

C O P Y

26 February 2002

Debra Villanueva
IDEC Pharmaceuticals Corporation
3030 Callan Road
San Diego
CA
92121

Subject: U.S. Patent No. 5776456
Your Ref : 1992-30-0029CP1D1/C2

Dear Ms. Vallanueva,

In response to your letter of 19 December 2001, we confirm that the maintenance fee due in respect of the above patent has been paid and the official receipt is enclosed for your records.

Yours very truly,

PILLSBURY WINTHROP LLP
Mariam Ardalan, International Dept.

37003/ 276465

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

909

M75MB

PILLSBURY WINTHROP LLP
1600 TYSONS BOULEVARD
MCLEAN VA 22102

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(h).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,776,456	183	880		08/476,275	07/07/98	06/07/95	04	NO	PAID

ITM NBR	ATTY DKT NUMBER
1	012712-155

**DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, D.C. 20231**

Exhibit D

Description of Significant Activities Undertaken During the Regulatory Review Period for Zevalin® and Applicable Dates for Such Activities

Chronology for BB-IND 4850
IDEC-Y2B8 Zevalin (ibritumomab tiuxetan)

DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
02/12/02	41	281	Pr. Am. CIP, New Inv. Changes	IDEC to FDA	L. Shelly for A. Wei submits CIP for 22 sites for 106-04 and 106-98, New Investigators for 106-98, Changes for 106-04 and 106-98 for 1572's and Informed Consent Forms. See study drug log.		
02/12/02	41	280	Info. Amend. CMC	IDEC to FDA	L. Shelly for A. Wei submits CMC information stating MDS Nordion has completed construction of a 2nd production suite and we make reference to MDS Nordion BB-MF-9175. C of A's included.		
02/05/02	41		Facsimile Emergency Use Request	IDEC to FDA	L. Shelly for A. Wei sent a fax to P. Bishop. January 28, 2002 telecon was the request to treat an emergency use patient with Zevalin. (modified protocol 106-98).		S. Fino
02/04/02	41	279	Prot. Amend. New Invest.	IDEC to FDA	S. Fino for A. Wei submits new investigator information for 106-98. **Add to study drug log - Ronald Weiner and Robert Bona, Farmington, CT.**	791172253391	S. Fino
02/04/02	41	278	Info. Amend. CMC	IDEC to FDA	S. Fino for A. Wei sent CMC info. This trial is being conducted to ensure availability of Zevalin to patients until the product is available commercially. Cof A's and KMI/Parexel Transmittal Form Project Deliverables.	791770545899	S. Fino
02/01/02	41	277	IND Safety Report	IDEC to FDA	S. Fino for A. Wei submits an initial written safety report for patient number 106-98-063-428. (initals CLA) Mfr. report number 000206.	790295829243	S. Fino
01/31/02	41		Facsimile	IDEC to FDA	S. Fino for A. Wei faxed a 7 day fax transmission IND Safety Report for patient 106-98-063-428 initials CLA.		S. Fino
01/29/02	41	276	IND Safety Report	IDEC to FDA	L. Shelly for A. Wei submits an initial written safety report for patient 106-98-106-189 (initials P-L). Mfr. report number 000204.	790290958700	S. Fino
01/28/02	41	275	Prot. Amend. New Invest.	IDEC to FDA	L. Shelly for A. Wei submits protocol amendment with new investigator information.	792482423415	S. Fino
01/23/02	41	274	Info. Amend. Clinical	IDEC to FDA	S. Fino for A. Wei sent an information amendment containing a synopsis for a patient who experienced an unexpected biodistribution during treatment with In-111 - decision not to treat with 90-Y.	790988237676	S. Fino

Chronology for BB-IND 4850
IDEC-Y2B8 Zevalin (ibritumomab tiuxetan)

DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
01/22/02	see Cross Ref. Binder		Fax	Diosynth to IDEC	Kathleen Payne of Diosynth - formerly Covance Biotechnology Services, Inc. sent a fax to John Dunn stating they are preparing a Type V DMF. Requesting copies of relevent sections of IDEC reg. filings. Their previous DMF was Type I. Company name change was as of July 2001 - but is same company, same location and same physical mfg. plant. Phone number 919-678-4482.		
01/17/02	41	273	Name & Address Change	IDEC to FDA	L. Shelly for A. Wei informs FDA that IDEC current fill/finish provider for Zevalin has change in name and address. DSM Catalytica Phar. Officially changed to DSM Pharm., Inc. effective 12/14/01.	791757820900	
01/04/02	41	272	Prot. Amend. New Invest. CIP	IDEC ot FDA	S. Fino for A. Wei submits CIP, New Investigator, and clinical info. for protocol 106-98. See study drug log.		
12/19/01	41	271	IND Safety Report	IDEC to FDA	S. Fino for A. Wei submits follow up safety information for patient 106-98-050-382 initials DGG. Report 000166.		
12/07/01	41	270	Cross Reference Letter	IDEC to FDA	L. Shelly for A. Wei submits letter authorizing cross reference in support of PS-IND - Investigator responsible: Issa Khouri, MD, MD Anderson Cancer Ctr., Houston, TX	792470915910	
11/30/01	41	269	Cross Reference Letter	IDEC to FDA	L. Shelly for A. Wei submits letter authorizing cross reference in support of PS IND. Investigator responsible: Anas Younes, M.D., MD Anderson Cancer Ctr., Houston, TX		
11/26/01	41	268	Cross Reference Letter	IDEC to FDA	L. Shelly for A. Wei submits letter authorizing cross reference for Ph 1/II Trial - Investigator responsible - James L. Murray, MD Anderson Cancer Center, Houston, TX. Norman Padre sending out the letter to the physician.		
11/19/01	41	267	IND Safety Report	IDEC to FDA	S. Fino for A. Wei sent an initial written report for patient 106-98-050-382 (pt. initials DGG). Protocol 106-98. Mfr. report number 000166.		
11/16/91	41		Fascimile	IDEC to FDA	S. Fino for A. Wei sent a fax submission of the initial written report for report for patient 106-98-050-382 (pt. initials DGG). Protocol 106-98. Mfr. rep. number 000166. Regular number submission to follow via hard copy on 11/19/01.		

Chronology for BB-IND 4850
IDEC-Y2B8 Zevalin (ibritumomab tiuxetan)

DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
11/12/01	40	266	Prot. Amend. New Invest.	IDEC to FDA	L. Shelly for A. Wei submits new investigator information for 106-98 - 4 new investigators. See Study Drug Log.		S. Fino
11/05/01	40	265	IND Safety Report	IDEC to FDA	S. Fino for A. Wei submits a follow up safety report for patient number 106-98-001-050 - (pt. initials DOS). Protocol 106-98 - Mfr. report number 000026.		S. Fino
10/30/01	40	264	Prot. Amend. New Invest.	IDEC to FDA	A. Cerny for A. Wei submits a protocol amendment with changes to form 1572 and informed consent and new investigators. - Protocols 106-04, 106-05, 106-06, 106-98		A. Cerny
10/29/01	40		Labeling Package Insert	IDEC to FDA	A. Cerny sent 2 sets of labels for package insert - both Ytrrium and Indium to the Information Management Team/FDA	792683642635	A. Cerny
10/22/01	40	263	End of Ph II pre-Ph III	IDEC to FDA	12 sets of pre-pivotal packets for end of Ph 2/pre-Ph 3 protocol. Requests confirmation of FDA meeting date of November 15, 2001 to discuss the proposed Phase III protocol.		S. Fino
10/16/01	40	262	IND Safety Report	IDEC to FDA	S. Fino for A. Wei submits a 15 calendar day initial written report for patient 106-98-001-050. (Initials DOS).		S. Fino
09/21/01	40	261	Prot. Amend. New Invest. CIP	IDEC to FDA	D. Mitchell for A. Wei submits new investigator information and a CIP for 13 investigative sites. - 106-04 and 106-98. See Study Drug Log.		A. Cerny
09/17/01	39		Voicemail	FDA to IDEC	R. Homaitabar leaves a voicemail for L. Shelly confirming the November 15 1-2:30 PST meeting for Pre-Phase III with the agency.		
09/10/01	39	260	Prot. Amend. New Invest.	IDEC to FDA	S. Fino for A. Wei submits new investigator information for 106-98.		S. Fino
09/06/01	39	259	Cross Reference Letter	IDEC to FDA	S. Fino for A. Wei grants authorization to allow review of the preclinical, clinical and CMC information within IND 4850 and MF-7087. Investigator responsible: Andres Forero, MD, Univ of Alabama.		S. Fino
09/05/01	39	258	Meeting Request	IDEC to FDA	S. Fino for A. Wei submits a request for a meeting with CBER Type B to discuss proposed phase II protocol.		S. Fino
08/23/01	39	257	Prot. Amend. New Invest.	IDEC to FDA	S. Fino for A. Wei submits CIP, New Investigator, and Changes to FDA Form 1572 for 106-04, 106-06, and 106-98.		S. Fino

Chronology for BB-IND 4850
IDEC-Y2B8 Zevalin (ibritumomab tiuxetan)

DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
08/13/01	39	256	Prot. Amend. New Invest.	IDEC to FDA	S. Fino for A. Wei submits new investigator information for 106-98.		S. Fino
08/10/01	39	255	Information Amendment: Clinical	IDEC to FDA	S. Fino for A. Wei submits copy of letter sent to all Zevalin investigators informing them of a potential safety issue	790129290850	S. Fino
07/09/01	39	254	Cross Reference Letter	IDEC to FDA	S. Fino for A. Wei submits a Letter of Cross Reference - Ruby Merideth, M.D., - Univ. of Alabama	790098472246	S. Fino
07/05/01	39	253	Emergency Use	IDEC to FDA	S. Fino for A. Wei submits clinical documentation for 3 patients treated on Emergency Use Protocols. 106-99-004-004, 106-99-003-003 and 106-99-003-005.	791606861241	S. Fino
07/03/01	39	252	Prot. Amend. New Invest, Change 1572 CIP	IDEC to FDA	L. Shelly for A. Wei submits new investigator information for 106-98 and changes in 106-03, 05,, 06 and 98. Also a CIP for 106-98	791604577375	A. Cerny
06/29/01	39	251	IND Safety Report	IDEC to FDA	S., Fino for A. Wei submits a 15 day initial written IND safety report for 106-98-064-195. Initials TJO 64 yr. old male. Report #4850-024	790092232606	S. Fino
06/20/01	39	250	Prot. Amend CIP, Clin. Info. Amend.	IDEC to FDA	S. Fino for A. Wei submits new investigator informaiton and a CIP for 8 sites and an approved revised consent doc. for 106-98.	790083708130	S. Fino
06/13/01	38 (only)	249	Prot. Amend CIP	IDEC to FDA	A. Wei submits a C.I.P. for 5 ongoing Zevalin studies. 106-03, 106-04, 106-05, 106-06 and 106-98. Consisted of two volumes - Sent 3 sets	790937827501	S. Fino
06/01/01	37	248	Emergency Use Protocol	IDEC to FDA	A. Wei submits a protocol, model informed consent and CRFS for a single patient. 37 yr. old male	791575622305	S. Fino
05/17/01	37	247	Prot Amend New Invest	IDEC to FDA	S. Fino for A. Wei submits new Investigator Information John Sweetenham, MD Univ. of CO Health Sciences Center, Denver, CO	790056708721	S. Fino
05/18/01	37	246	Cross Reference Letter	IDEC to FDA	S. Fino for A. Wei submits a Letter of Cross Reference - Susan O'Brien, M.D., - MD Anderson	790055643080	S. Fino

Chronology for BB-IND 4850
IDEC-Y2B8 Zevalin (ibritumomab tiuxetan)

DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
05/17/01	37	245	Prot Amend New Invest. Clin. Info Amd	IDEC to FDA	A. Wei submits new investigator info, change in protocol, changes to 1572 , IRB approvals, and revised informed consent documents. See study drug log.	791562249723	S. Fino
04/30/01	37	244	Prot Amend New Invest.	IDEC to FDA	A. Wei submits a Protocol Amend. New Investigators and C.I.P. - See Study Drug Log.	792412258624	S. Fino
04/26/01	37	243	IND Safety Report	IDEC to FDA	A. Wei submits an IND Safety Report: Follow up - Patient 106-06-018-036 initials WFD - Report number 4850-17A	791539896863	S. Fino
04/23/01	36	242	Annual Report	IDEC to FDA	S. Fino for A. Wei submits annual report covering period March 2000 thru February 2001. Study Reports, Investigational Brochure and Stability included. (2 Volumes).	790033293057	S. Fino
04/19/01	35	241	Info. Amd. Clinical	IDEC to FDA	S. Fino for A. Wei submits an information amendment of meeting abstracts.	790926994684	S. Fino
04/06/01	35	240	Emergency Use	IDEC to FDA	S. Fino for A. Wei submits three protocols for Emergency Use of an IND. 106-98	791522318013	S. Fino
04/04/01	35	239	Info. Amend. Pharm/Tox	IDEC to FDA	S. Fino submits an information amendment Pharm/Tox. Containing preclinical study reports. AS0175 and AS0176.	792407448365	S. Fino
03/26/01	35	238	Pro. Amend.: New Investigator	IDEC to FDA	L. Shelly for A. Wei Submits a protocol amendment consisting of 6 additional new investigators for 106-98.	790921467516	S. Fino
03/21/01	34	No Ser #		IDEC to FDA	Emergency use IND	791506199769	S. Fino
03/16/01	34		Telecon for Emergency Use	IDEC to FDA	Request to treat three patients (BB-IND 4850) on an emergency use basis status post autologous stem cell transplantation.		
03/07/01	34	237	Prot Amend New Invest.	IDEC to FDA	L. Shelly for A. Wei submits a protocol amendment consisting of 3 additional new investigators for 106-98.	791993428396	S. Fino
03/06/01	34	236	Prot. Amend CIP	IDEC to FDA	S. Fino for A. Wei submits a protocol amendment - CIP (Amend. #3) for 106-98 - Amended to incorporate addt'l safety parameters and administrative changes.	792401634918	S. Fino
02/21/01	34		Telecon Minutes	IDEC Internal	L. Shelly minutes from Pre-BLA meeting with the FDA concerning clinical telecon re: revised calibration protocol for Amend. #3, Protocol 106-98.		

Chronology for BB-IND 4850
IDEC-Y2B8 Zevalin (ibritumomab tiuxetan)

DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
02/13/01	34		Telecon Minutes	IDEC Internal	L. Shelly minutes from Pre-BLA meeting with the FDA concerning clinical telecon re: addition of indium to protocol 106-98. This is also in Zevalin BLA 125019/0 chronology.		
02/01/01	34	235	Pro. Amed: CIP, New Investigator, Change 1572	IDEC to FDA	L. Shelly for A. Wei submits a protocol amendment consisting of new investigator info. for 3 sites, protocol 106-98, CIP for 106-04 & 05, and site documentation for 3 sites for 106-05 and 106-98. See study drug log.	790461874200	A. Cerny
01/30/01	34	234	IND Safety Report	IDEC to FDA	S. Fino for A. Wei submits follow up safety information for three of the four previously reported cases of prolonged pancytopenia. The 4th case involved a fatal event for which no further data is available, report was sent via fax to Drs. P. Bishop and G. Mills on 1/29/01. Patients: 106-98-019-049 (BMM), 106-98-012-104 (K-P), 106-05-005-013 (MMS).	792656385555	S. Fino
01/29/01	34		Facsimile	IDEC to FDA	S. Fino for A. Wei sent a fax submission enclosing follow up safety information for the 3 of 4 reported cases of prolonged pancytopenia. Fax was 14 pages.		
01/24/01	34		Facsimile	IDEC to FDA	S. Fino for A. Wei sent a fax submission to P. Bishop and G. Mills. As a result of a safety report of pancytopenia, IDEC is proposing an amendment to the open label Protocol 106-98. Attached are the proposed revised portions of the protocol. Fax was 19 pages.		
01/23/01	34	233	Cross Reference Letter	IDEC to FDA	S. Fino for A. Wei submits a cross-reference letter for A Phase I/II Study of Zevalin□ for Post Transplant Relapses of B-Cell NHL. Investigator is **Julie M. Vose Univ. of Nebraska Medical Center., Omaha, NE.**	790453293623	S. Fino
01/17/01	34	232	Pro. Amend.: New Investigator Chgs to 1572	IDEC to FDA	B. Powell for A. Wei submits a protocol amendment consisting of three new investigators and one change of Form 1572.	790907571920	S. Fino

Chronology for BB-IND 4850
IDEC-Y2B8 Zevalin (ibritumomab tiuxetan)

DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
01/12/01	34		FDA Telecon	IDEC & FDA	**IDEC:** S. Fino, B. Leigh, P. Multani, L. Shelly, A. Wei. **FDA:** G. Mills, P. Bishop, M. Andrich. FDA's request for telecon to discuss a safety report from 106-98. G. Mills expressed concern that 4 patients have experienced prolonged pancytopenia and whether a pattern could be developing.		
01/04/01	34	231	Pro. Amend.: CIP, New Investigator Change 1572	IDEC to FDA	S. Fino for A. Wei submits a Protocol Amendment – Change in Protocol for 10 investigative sites for 106-04 & 106-06, change of principal investigator for one site 106-04, and 10 changes to 1572 for 106-04 & 06. See Study Drug Log.	790438366872	A. Cerny
12/22/00	34	230	Information Amendment: GMP Organization Chart	IDEC to FDA	L. Shelly for A. Wei sent an updated organizational chart reflecting recent changes to the GMP management team at IDEC. – Departure of J. Geigert previous vice-president of Quality, J. Leonard current vice-president of Preclinical Product Development will assume the additional role of Acting V.P. of Quality effective 12/21/00. Also P. Grint will assume the position of Chief Medical Officer and Sr. VP of Clinical Research and Development replacing A. Grillo-Lopez upon his retirement.		B. Hilal
12/20/00	34	229	IND Safety Report	IDEC to FDA	S. Fino for A. Wei submits a 15 day initial written report for patient 106-98-012-104 (initials K-P) Report submitted via a 15 calendar day fax because it involves an event that is serious and unexpected. – FDA 3500A forms attached. AE 4850-023.		S. Fino
12/20/00	34		Voicemail	FDA to IDEC	Dr. G. Mills left a voicemail for A. Wei regarding a telecon stating he has a call into R. Sparks but he hasn't returned call as of yet. – No code number coming along		
12/12/00	34		Voicemail	FDA to IDEC	M. Shapiro, CBER, left voicemail for A. Wei with a question. How does a user order Zevalin to get the yttrium, is it separately or through IDEC?		
12/07/00	34		Voicemail	FDA to IDEC	D. Trout left voicemail for A. Wei regarding validation and it was received exactly as sent. She needed verification of container closure in master file for Catalytica for the sterilization/validation depyrotination data. Nothing to do with media cell data. She wants info by Monday 12/11/00.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
12/06/00	34		Voicemail	FDA to IDEC	D. Trout left voicemail for A. Wei regarding a validation fax. She only received 6 of 8 pages and is concerned about getting order configuration and sterilization validation.		
12/01/00	33	228	Pro. Amend.: CIP, Change 1572, Clin. Info. Amend. IRB Consent form	IDEC to FDA	S. Fino for A. Wei submits a protocol amendment with addition of two new investigators for 106-98 – changes to FDA 1572 and Informed Consent documents for 4 sites.		S. Fino
11/29/00	33		Voicemail	FDA to IDEC	Dr. G. Mills left voicemail for A. Wei regarding setting up telecon with Rick Sparks. on indium issues and until Antonio and Pat get themselves squared up he decided not to setup a telecon.		
11/28/00	33		Telecon	IDEC to FDA	**IDEC:** Bryan Leigh, John Leonard, Antonio Grillo-López, Pratik Multani, Alice Wei, Augusta Cerny. **FDA:** M. Andrage, Felippe Bishop, Leon Eps, George Mills (CBER). Telecon was held to discuss the Zevalin BLA and the NCI IND.		
11/22/00	33	227	IND Safety Report	IDEC to FDA	S. Fino for A. Wei submits a follow up safety report for patient number 106-98-019-049 – Female, 55 yr old with stage IV. (Initials BMM). A 7-day facsimile safety report regarding an Adverse Event of prolonged pancytopenia was sent to G. Mills on 9/7/00. The following day an initial report was submitted. FDA Form 3500A is enclosed. – AE#4850-022A.		S. Fino
11/21/00	33		Voicemail	FDA to IDEC	Phillipe Bishop left voicemail for C. Palahang stating he and Dr. Mills had two additional issues regarding the BLA application and wanted to discuss before Thanksgiving holiday.		
11/21/00	33		Voicemail	FDA to IDEC	P. Bishop left voicemail for A. Wei - stating he and Dr. Mills had two additional issues regarding the BLA application and wanted to discuss before Thanksgiving holiday.		
11/17/00	33		Voicemail	FDA to IDEC	M. Noska left voicemail for C. Palahang regarding setting up a telecon for Monday around 3 o'clock EST for BLA/ Zevalin with D. Kim. He knows Alice is out of the office and states if there is any way Alice/Leslie or both would be helpful.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
11/17/00	33		Voicemail	FDA to IDEC	D. Trout left voicemail for C. Palahang trying to get a hold of a production schedule and she knew Alice is out until the 22nd. She wanted to get it by Monday the 20th.		
11/09/00	33		Voicemail	IDEC to CBER	G. Mills emails A. Wei has questions/concerns in terms of a letter of cross reference coming in for an IND with Alice's signature on it. Concerns for its material use.		
11/09/00	33	226	Clinical Info. Amendment	IDEC to FDA	S. Fino for A. Wei submits a Clinical Info. Amendment consisting of meeting abstracts. 5 abstracts total.(2 oral, 3 poster)		S. Fino
11/06/00	33		Telecon	IDEC to FDA	L. Shelly called M. Noska to ask him for further information about the letter that IDEC received from CBER on 10/27/00. The letter stated that the annual report for Zevalin had not been received. Mike confirmed that it had on September 29, 20000 #221 and is recorded in the system.		
10/31/00	33	225	Pro. Amend.: New Investigator Clinical Info. Amended	IDEC to FDA	S. Fino for A. Wei submits a Protocol Amendment to Protocol 106-98 with new investigators and a Clinical Info. Amendment with a revised IRB consent form.		S. Fino
10/27/00	33	224	Response to request for information	IDEC to FDA	S. Fino for A. Wei submits a response to FDA request for information regarding survey procedures and results.The request was made at the Zevalin Pre-BLA meeting.		S. Fino
10/27/00	33		Annual Report Request	FDA to IDEC	M. Noska of CBER sends letter to A. Wei requesting an annual report to be submitted within 30 days.		
10/24/00	33	223	Pro. Amend.: New Investigator Revised 1572, Clinical Info. Amend.	IDEC to FDA	S. Fino for A. Wei submits a protocol Amend. to Protocol 106-98. New Investigators and Revised 1572. Clinical Info. Amend. with an IRB approved consent form revision.		S. Fino
10/17/00	32		Fax	TRI/CTEP to IDEC	P. Queen faxed to A. Grillo-Lopez per Dr. Shoemaker of NCI/RAB an Initial written report for MoAb IDEC C2B8. AE Ticket # 1001447 (IND#7028/FDA serial #052).		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
10/16/00	32		Letter	IDEC to FDA	Copy of original letter to J. Siegel, M.D. authorizing cross-reference to all information contained in the BLA for Zevalin. Copy sent to Tim Nason Only – Not to Jay Siegel.		
10/12/00	32		Voicemail Message	FDA to IDEC	M. Fauntleroy left a message for A.Wei regarding a pilot program that is moving out of the Agency for the electronic representation of AE's utilizing ESTRI Gateway. Electronic submissions will come in over the wire that will catalog the AE reports for therapeutic biological entities in CBER for the therapeutic product and CDER. Wants to discuss other specifics of the program and see if there's an overall intrest at IDEC in moving forward.		
10/09/00	32	222	CALA-Imaging Demo.	IDEC to FDA	A. Wei to M. Fauntleroy submits CALA Imaging Demonstration. 2 CD ROMs included. Also included are the additional data fields previously requested by the agency.		D. Kim
10/04/00	32		Meeting Summary	FDA to IDEC	M. Noska sends to A. Wei a summary of meeting minutes from meeting held on July 18, 2000. 9 pages.		
09/19/00	32		Voicemail	FDA to IDEC	M. Fauntleroy left message for A. Wei on 9/19/00. Calling in regards to Monday. Regrettably, George didn't mention that he had morning and afternoon reports, so Monday is a no go. Would appreciate some time on Tues., Wed. or Thurs. Give me a call. Sorry if this is becoming convoluted. Thanks		
09/29/00	32	221	Annual Report	IDEC to FDA	S. Fino for A. Wei submits Annual Report for the reporting period for March 1999 through February 2000.		S. Fino
09/28/00	32	220	Info. Amend. CMC Response to FDA RFI	IDEC to FDA	L. Shelly for A. Wei, submits Info. Amend. CMC for BB-IND 4850. Response to FDA Req. for info. On August 24, 2000 a telecon between IDEC and CBER was held. Enclosed are responses to FDA requests for CMC information that were discussed. FDA requests are in bold – followed by response.		L. Shelly
09/20/00	32	219	Pro. Amend.: New Investigator Chgs to 1572	IDEC to FDA	S. Fino for A Wei submits Protocol Amend. to Protocol 106-98 new investigators and changes to form FDA 1572 for one site		S. Fino

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
09/08/00	32	218	IND Safety Reports	IDEC to FDA	S. Fino for A. Wei submits a 7 day fax transmission IND Safety Report for patient #106-98-019-028 (initials NJT) and a 15-day Initial Written Report for patient 106-98-019-049 (initials BMM), Both patients were treated with Y2B8 under the same protocol and experienced prolonged pancytopenia. These copies were faxed to George Mills on 9/7/00.		S. Fino
09/07/00	32	217	Gen'l Corr.	IDEC to FDA	A. Wei submits hardcopy of email to M. Fauntleroy containing telecon minutes from Sept 1, 2000 Telecon. Attached is random patient list for submission of digitized CT films.		A. Wei
09/07/00	32		Email	IDEC to FDA	A. Wei emailed M. Fauntleroy (CBER) agenda for scheduled telecon on 09/08/2000. Attachments also include the contents of serial #217 (telecon minutes from 09/01/2000, and random patient list for the submission of digitized CT films).		
09/06/00	32	216	Pro. Amend.: New Investigator Chgs to 1572	IDEC to FDA	A. Cerny for A. Wei submits Protocol Amend. Changes In 1572 for 3 sites for Protocols 106-06 and 106-98 and new investigator for one site for Protocol 106-98		A. Cerny
09/06/00	32		Voicemail	FDA to IDEC	M. Fauntleroy to D. Kim regarding telecon scheduled for 7 to 8 Pacific time, 10 to 11 eastern. Dr. Mills and P. Bishop will attend to discuss imaging demo. Request to provide record of understanding/contract record from last telecon & discussion points for for this telecon via email.		
09/06/00	32		Voicemail	FDA to IDEC	M. Fauntleroy to A. Wei Re: telecon scheduled for Friday at D. Kim's request. Time set for 7 to 8 pacific time. G. Mills and P. Bishop will be attending. Reminder to send record of contract, understandings of last telecon, and agenda for this telecon.		
08/31/00	32	215	Request for Telecon	IDEC to FDA	L. Shelly for A. Wei requests a telecon in response to discussion held on 8/12/00 to resolve issues associated with content & format of the Clinical Section of the Zevalin BLA. Proposed Agenda included.		L. Shelly

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
08/30/00	31	214	Pro. Amend.: Chgs to 1572	IDEC to FDA	S. Fino for A. Wei submits Protocol Amend. Change in protocol for 4 sites for Protocols 106-05 and 106-06. Changes in form FDA 1572 for 13 sites for Protocols 106-03, 106-04, 106-05, 106-06 and 106-98. See Study Drug Log.		S. Fino
08/18/00	31	213	General Correspond. CALA Demo (revised)	IDEC to FDA	A. Wei submits a General Correspondence submission of the revised CALA demonstration to M. Fauntleroy as requested in a telecon on July 25, 2000. All FDA comments have been incorporated.		J. Pool
08/18/00	31		Facsimile	FDA to IDEC	M. Noska sent a fax request to L. Shelly & A. Wei for CT Images- a Random Patient/Response Verification list is attached to cover page – from 1-41.		
08/15/00	31	212	Pro. Amend.: CIP, Chg. Invest., Chg. 1572.	IDEC to FDA	L. Shelly for A. Wei submits a protocol amendment consisting of Chg. In form 1572 for 106-03 and a C.I.P. and change in investigator for 106-06.		S. Fino
08/09/00	31	211	General Corresp. Letter of Understand-ing	IDEC to FDA	L. Shelly for A. Wei sent letter stating that on 7/18/00 a pre-BLA meeting was held to discuss the filing under the auspices of FDA's Fast Track Program. During the meeting, FDA accepted the general format and the clinical data content supporting the patient population. If both agree on "rolling BLA" IDEC could file digitized CT films and nuclear medicine images with the last section of BLA		S. Fino
08/09/00	31	210	Pro. Amend.: New Invest.- C.I.I./C.I.P.- C.I.F1572-Clin. Info Amend. IRB Approval	IDEC to FDA	S. Fino for A. Wei submits protocol amend. changes for new investigator for phase II Protocol 106-98 other changes on Protocols 106-04 Phase III. See study drug log.		A. Cerny

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
08/03/00	31	209	Info Amend: CMC Resp. to FDA: RFI	IDEC to FDA	L. Shelly for A. Wei sent letter stating on 7/18/00 a pre-BLA meeting was held between CBER & IDEC to discuss our BLA. Enclosed are our responses to FDA requests for CMC information that were discussed at the meeting. FDA requests are in bold – followed by our response. IDEC also requests the scheduling of a telecon with Marjorie Shapiro and Leon Epps to discuss the CMC information within this submission.		L. Shelly
07/31/00	31	208	Response (includes Facsimile)	IDEC to FDA	A. Wei submits response to telecon FDA Request for Information, specifically, a list of all patients from trials 106-04 and 106-06 with which FDA will generate list of required CT scans for BLA. **Faxes are filed with this submission.**		L. Shelly
07/31/00	31	207	Revised Request	IDEC to FDA	A. Wei submits Revised Request for Rolling BLA status. Includes draft table of contents for the major sections of the proposed BLA.		D. Kim
07/28/00	31		Voicemail	FDA to IDEC	M. Noska returns A. Wei's call. Requests call back.		
07/28/00	31		Facsimile	IDEC to FDA	A. Wei faxes draft of an unnumbered submission general correspondence: Letter of Understanding regarding agreements reached at July 18 pre-BLA meeting.		
07/28/00	31		Telecon	IDEC to FDA	IDEC phones M. Noska in follow up to the pre-BLA meeting to discuss the issue of CT scans to be provided for the clinical section of the Zevalin BLA.		
07/27/00	30	206	Pro. Amend.: Clinical Info Amended	IDEC to FDA	A. Wei submits a protocol amendment with changes in form FDA 1572 for 15 sites for PIII Protocol 106-04. A protocol amendment with IRB approvals for changes in protocol for 10 sites for the PIII protocol 106-04, clinical information amendment with annual update IRB approval letter for 1 site and an IRB approval for revised consent form for 1 site. See Study Drug Log.		A. Cerny
07/26/00	30		Voicemail	FDA to IDEC	M. Noska calls A. Wei to follow up re: submission of films and images. Will call again.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
07/25/00	30	205	CMC amend.	IDEC to FDA	On 7/14/00 a teleconference was held between Tim Nason, Ph.D. (MDS Nordion) and M. Noska, CBER to discuss a change in acceptance limit for the Bacterial Endotoxin (LAL-gel clot) test used as part of the release criteria for Yttrium-90 Chloride Sterile Solution. It is used in IDEC's investigational product Zevalin for the treatment of NHL. IDEC plans to initiate patient treatment with yttrium from MDS Nordion during the week of July 24, 2000.		B. Powell
07/25/00	30		Telecon	IDEC to FDA	M. Fauntleroy expresses to D. Kim and others FDA's thoughts on the revised Zevalin CALA demo. The README and Items 2, 3, 5, 6, 8, 12, and 15 are discussed.		
07/21/00			Telecon	IDEC to FDA	Daniel Kim phone Michael Fauntleroy requesting guidance for the design of an electronic CRF.		
07/19/00	30	204	Pro. Amend.: New Invest., C.I.P., Clinical Info Amended (Rev. Inform. Consent)	IDEC to FDA	S. Fino for A. Wei submits a protocol amendment and a clinical information amendment.		S. Fino
07/18/00	30		Memo of Pre-BLA	IDEC Internal	D.Kim, L. Shelly & A. Wei combined clinical Pre-BLA minutes for meeting. See actual document for attendees – both IDEC and FDA – Introduction, Exec. Summary, Clinical, CMC and General Comments – Signature page included of participants.- Also reduced slide presentation.		
07/17/00	30	203	CALA Demo	IDEC to FDA	A. Wei submits to M. Fauntleroy REVISED demonstration CALA. The original CALA demo was submitted in #189. Revisions were requested in a June 29, 2000 telecon with Fauntleroy. Copy of CD in CD Library.		D. Kim
07/17/00	30		Voicemail	FDA to IDEC	M. Fauntleroy leaves message for A. Wei requesting feedback on target submission date for revised demo. (Demo mailed today).		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
07/07/00	30		Facsimile	IDEC to FDA	A. Wei send fax to M. Noska/CBER enclosing the supplemental information for the pre-BLA meeting and the request for a rolling BLA – same as submission #202.		
07/07/00	30	202	Supplement. Info for Pre-BLA Mtg.	IDEC to FDA	A. Wei submits supplemental info for the 7/18/00, pre-BLA meeting for Zevalin. During discussions with FDA reviewers on 6/9 and 6/30/00 several new issues associated with the content and format of the clinical section have arisen. 1. CT Scans, 2. Nuclear Medicine Images, 3.LEXCOR Evaluation of Disease Progression, 4. Case Report Forms, and 5. Datasets for Protocol 106-03.		L. Shelly
07/07/00	30	201	Request for Review	IDEC to FDA	A. Wei sent request for Review of Portions of an Application to Jay Siegel stating that IDEC is proposing to file a BLA for our product Zevalin. June 4, 2000 Zevalin was granted Fast Track Designation, thus we also wish to request that IDEC be allowed to file portions of the application before the complete application is available under the "Rolling BLA Review" process. The specific sections of the appl. Along with a proposed schedule are found in Table 1. We propose to submit the last portion by 11/15/00. (No 1571was sent with this submission).		L. Shelly
07/05/00	30	200	Cross Reference Letter	IDEC to FDA from NCI	Susette sends letter of cross-reference with regard to new IND from National Cancer Institute. Copy send to Sherry Ansher at Regulatory Affairs, CTEP, Rockville, MD.		S. Fino
06/30/00			Telecon	IDEC to FDA	**IDEC:** Daniel Kim, Bryan Leigh, Pratik Multan, Leslie Shelly, David Shen, Alice Wei. **FDA:** Michael Fauntleroy and George Mills. A teleconference was held in response to an urgent request made by Michael Fauntleroy on the evening of Thursday, June 29, 2000		
06/30/00	30		Letter & CD Rom	IDEC to Schering	D. Kim sends W. Shultz, Shering AG, a CD-ROM containing numerous Zevalin application files, including Non-clinical, CMC, and Clinical sections.		
06/29/00	30	199	CMC Amendment	IDEC to FDA	A. Wei submits CMC amendment for Nordion Yttrium		B. Powell

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
06/29/00	30		Voicemail	FDA to IDEC	M. Fauntleroy and G. Mills leave message for A. Wei requesting telecon time to discuss digitizing of images and dosimetry images to be included in BLA. He stresses the importance of discussing this further.		
06/28/00	30		Email	IDEC to FDA	D. Kim writes M. Fauntleroy to confirm telecon scheduled for June 29 1:30pm EST to discuss Zevalin CALA demo.		
06/28/00	30	198	New Investigators and C.I.P.	IDEC to FDA	A. Wei submits New Investigators and Change in Protocol . Three new investigators for Protocol 106-98: Also a change in protocol for investigative site #062,		S. Fino
06/28/00	30		Letter & CD	IDEC to CDE	D. Kim sends Dr. Richard Sparks, CDE Dosimetry Services, a CD-ROM containing Protocols 106-06, 106-05, and 106-04.		
06/27/00	30		Email	Schering AG to IDEC	M-C. Clarke writes A. Wei with attached paperwork from Pre-Submission Meeting at EMEA. She promises minutes as soon as they are finalized by EMEA.		
06/26/00	30		Telecon	IDEC/FDA	IDEC and FDA representatives discuss Emergency Use patient and Content and Format of the Clinical Section of the BLA. Minutes recorded by Daniel Kim.		
06/23/00	30		Telecon	IDEC to FDA	L. Shelly calls S. Jerian, FDA, to she if she rec'd info sent 6/18, and whether she can have telecon on 6/30.		
06/23/00	30		Telecon	FDA to IDEC	S. Jerian, FDA, calls L. Shelly. She has not yet rec'd info sent 6/18, but she is available for telecon 6/30.		
06/22/00	30		Telecon	IDEC/FDA	L. Shelly speaks with G. Mills, FDA, regarding when he will get a Pre-BLA Meeting package (2nd set, additional info). The also discuss the possibility of another telecon next week.		
06/20/00	30	197	Pro. Amend.: New Investigator and C.I.P.	IDEC to FDA	A. Wei submits protocol amendment with two new investigators for Protocol 106-98		A. Cerny

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
06/20/00	30	196	Additional Information	IDEC to FDA	A. Wei submits additional information for scheduled Pre-BLA meeting. Package includes: most recent amendments for protocols 106-04 and -06, LEXCOR Charter, statistical and analytical plans for trials 106-04 and -06, and rationale for inclusion of SAS datasets. Protocols were submitted both in paper and on one CD-ROM, which is filed in CD-ROM archive.		L. Shelly
06/20/00	30		Voicemail	FDA to IDEC	G. Mills calls to say he is documenting the single patient exemption as a non-Hodgkin's lymphoma patient rather than large cell lymphoma.		
06/19/00	29	195	Facsimile	IDEC to FDA	L. Shelly for A. Wei submits request for authorization for emergency use. This fax reminds FDA of 6/9 telecon and informs them that FedEx submission for this Emergency Use is going in today.		
06/19/00	29	195	Emergency Use	IDEC to FDA	A. Wei submits documentation of Emergency Use of Investigational New Drug, Protocol 106-99		S. Fino
06/16/00	29		Voicemail	FDA to IDEC	M. Noska called to say he received pre-BLA package and that M. Fauntleroy received the CALA demo.		
06/15/00			Voicemail	IDEC to FDA	L. Shelly leaves message with M. Noska, FDA, saying that we submitted a pre-BLA meeting packages. She also asks if we should resubmit another CALA demo, because apparently M. Fauntleroy didn't receive it, despite our Fed Ex tracking showing delivery.		
06/15/00	29	194	Memoran-dum	IDEC to FDA	A. Wei submits memorandum of 4/11/00 teleconference with CBER to discuss IDEC's strategy for obtaining approval of its Commercial Manufacturing Facility as multi-product facility.		S. Fino
06/15/00	29	193	Pre-BLA Meeting Package	IDEC to FDA	A. Wei submits Pre-BLA meeting request and package. The meeting is scheduled for Tuesday, July 18, from 1-3 PM.		S. Fino
06/12/00	28	192	Initial Written Safety Report	IDEC to FDA	A. Wei submits Safety Report Initial Written Report for patient number 106-03-003-211 (S-R), who was in Protocol 106-03, and who died of myelogenous leukemia two years after Y2B8 therapy.		S. Fino

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
06/09/00	28		Telecon	IDEC to FDA	IDEC and FDA representatives discuss Zevalin Emergency-Use Patient and Zevalin BLA Clinical Section		
06/09/00	28		Facsimile	FDA to IDEC	M. Noska writes A. Wei to inform her that Y2B8 has been approved for Fast Track development status.		
06/09/00	28		Facsimile	IDEC to FDA	S. Fino faxes G. Mills, CBER, with the agenda and list of attendees for the teleconference scheduled for Friday, June 7 at 1pm. Agenda includes Emergency Use patient and content and format of clinical BLA sections.		
06/07/00	28		Voicemail	FDA to IDEC	K. Schneider, FDA, calls A. Wei, apparently responding to a question from Wei. She says she doesn't know the answer and has no new information, but "they're working on it."		
06/06/00	28		Voicemail	FDA to IDEC	M. Noska calls A. Wei to say he is returning her call regarding fast track review. He states that a letter has been sent, he can fax it if requested, and is willing to discuss any aspect of the letter.		
06/06/00	28		Emails	IDEC / FDA	Exchange between D. Kim and M. Fauntleroy. Kim requests a meeting to discuss some CALA topics. Fauntleroy declines, stating that he has not received adequate materials for such a meeting. Kim replies with an apology, stating that such materials were sent and documenting shipping information.		
06/05/00	28	191	Safety Report Follow Up	IDEC to FDA	A. Wei submits Safety Report Follow Up to Initial Written Report sent in Serial # 185. The patient expired on May 19, 2000.		S. Fino
06/05/00	28		Letter	FDA to IDEC	G. Jones writes A. Wei to inform her that Y2B8 has been approved for Fast Track development status.		
06/05/00	28		Facsimile	FDA to IDEC	M. Noska faxes L. Shelly a meeting announcement for July 18, 1 - 3pm, to discuss proposed BLA submission.		
06/01/00	28	190	Pro. Amend.: New Investigator, Clinical Info Amended	IDEC to FDA	A. Wei submits Protocol and Clinical Info Amendment with the following: The addition of 5 new investigators to Protocol 106-98:		S. Fino

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
06/01/00	28		Email	IDEC to FDA	D. Kim request a telecon with M. Fauntleroy to have an informal discussion re: Zevalin BLA Filing		
05/30/00	28		Voicemail	FDA / IDEC	D. Kim leaves message for M. Fauntleroy, FDA, to call him back. M. Fauntleroy calls and Kim and informs him the FedEx tracking number for Zevalin CALA CD-ROM submitted a week prior. Fauntleroy expresses timeline concerns; Kim assures him efforts are being made to resolve outstanding issues.		
05/26/00	28	189	CALA demo CD's	IDEC to FDA	D. Kim submits to M. Fauntleroy, FDA, CDs containing the Computer-Assisted License Application (CALA) demonstration, which includes representative examples of all major pieces of the BLA.		D. Kim
05/23/00	28		Telecon	FDA to IDEC	L. Shelly discusses with Mike Noska, FDA, and dates for the pre-BLA meeting. Noska still has not confirmed a date but is leaning towards June 22. Noska will try to call back 5/24.		
05/19/00	28		Facsimile	IDEC to FDA	L. Shelly faxes M. Noska requested copies of the agenda and participant list for the upcoming pre-BLA meeting (Type B) for Zevalin.		
05/17/00	28		Voicemail	FDA to IDEC	M. Fauntleroy leaves message for A. Wei. He looks forward to talking to Alice and Daniel Kim afternoon May 18.		
05/17/00	28		Voicemail / Telecon	IDEC / FDA	A. Wei leaves message for M. Fauntleroy, FDA, and requesting call back. Fauntleroy calls her, D. Kim joins telecon. They all discuss submission of a demo CALA, scheduling telecons to resolves outstanding issues, and which SAS Version the FDA is using.		
05/12/00	28		Voicemail	FDA to IDEC	G. Mills calls A. Wei to say he received the fax and it was "perfect and we're fully on schedule and on track."		
05/11/00	28	188	Response RFI	IDEC to FDA	L. Shelly submits information on the objectives of the pre-BLA meeting. ORR data are summarized here. Shelly requests meeting date of June 22 or 27, and requests M. Fauntleroy's presence.		L. Shelly
05/10/00	28		Voicemail	FDA to IDEC	G. Mills calls A. Wei and leaves phone number at which he should receive a fax he is currently expecting from IDEC.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
05/10/00	28	187	Pro. Amend.: C.I.P. & Change Form FDA 1572	IDEC to FDA	A. Wei submits New Investigators, Change in Protocol and Change for form FDA 1572. The following investigators are added to Protocol 106-98:		S. Fino
05/10/00	27	186	Response to Request	IDEC to FDA	Official mailed version of 5/9 fax.		
05/09/00	27	186	Response to Request Facsimile	IDEC to FDA	A. Wei submits supplemental info regarding responder statistics requested by FDA in support of request for Fast Track status.		L. Shelly
05/08/00	27	185	IND Safety Report	IDEC to FDA	A. Wei submits IND Safety Report: Initial Written Report for patient number 106-05-002-011 (Initials K-B), enrolled in Protocol 106-05.		S. Fino
05/05/00	27		Telecon	IDEC and FDA	B. Leigh, P., C. White, and S. Fino held telecon with G. Mills (FDA) to discuss three safety reports of myelodysplasia. IDEC explained what has been done and what we plan to do to keep ourselves, investigators, and patients informed about the potential causes and degree of this risk. G. Mills was supportive of our plans.		
05/01/00	27	184	Cross Reference Letter	IDEC to FDA	A. Wei authorizes access to BB-IND 4850 in support of an Investigator Sponsored IND, containing the protocol entitled "Primary Central Nervous System Non-Hodgkin's Lymphoma (PCNSL): A pilot Trial of Yttrium Labeled Anti CD20 Antibody (Y2B8) for Patients with New or Relapsed PCNSL." Gregory Wiseman, MD, Mayo Clinic, Rochester, NY.		S. Fino
05/01/00	27		Voicemail	FDA to IDEC	G. Mills (FDA) leaves message for A. Wei following up on the adverse event reporting the AML patient with Zevalin. He has suggestions for general course of action. Asks for call back re: informed consent, says otherwise everything submitted so far looks appropriate.		
04/28/00	27	183	Safety Report	IDEC to FDA	Official FedEx copy of fax sent 4/27/00.		S. Fino

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
04/27/00	27	183	Faxed IND Safety Report	IDEC to FDA	A. Wei faxes to G. Mills an IND safety report for a patient in IDEC 106-06 who exhibited myelodysplasia. Patient #106-06-018-036.		S. Fino
04/24/00	27		Voicemail	FDA to IDEC	Dr. J. Tiwari leaves message for D. Shen explaining that got error messages trying to run some some of the SAS programs we sent. He wonders if it is because he is using SAS Version 8. He requests call back.		
04/14/00	27	182	Pro. Amend.: Clinical Info Amended	IDEC to FDA	A. Wei submits protocol amendment and clinical info amendment consisting of: the addition of Gregory Wiseman, M.D. and Thomas Witzig, M.D., Mayo Clinic, Rochester, NY, to Protocol 106-98.; and a change in protocol.		S. Fino
04/11/00	27		Telecon	FDA/IDEC	M. Noska (FDA) called Leslie Shelly to confirm receipt of Fast Track request, and request for pre-BLA meeting. Fast Track is currently under evaluation. Noska says that before meeting request can be processed, FDA must have results from the primary endpoint of the trial. L. Shelly promised to relay this to IDEC and then get back to him.		
04/10/00	27	181	New Investigator Change in Protocol	IDEC to FDA	L. Shelly (for A. Wei) submits addition of two investigators to Protocol 106-98; a change in protocol for one investigative site; a revised Form 1572 for one investigative site.		S. Fino
04/06/00	27		Email	IDEC to FDA	D. Kim emails M. Fauntleroy with an update of IDEC's plans for Zevalin filing. If rolling process is approved, first submission will occur at the end of June. At least 90% of BLA will be electronic.		
04/05/00	27		Telecons	IDEC Internal	D. Kim documents two teleconferences with Michael Fauntleroy regarding IDEC's plans for submission of Zevalin CALA. M. Fauntleroy expresses concern that IDEC has not yet filed a demo. Kim explained IDEC's reasoning. Fauntleroy additionally stated that demo must include plans regarding submission of CT scan data (films).		
04/04/00	27	180	Fast Track/Rolling Request	IDEC to FDA	A. Wei requests Fast Track designation for Zevalin. Supporting documents included. She also requests a rolling BLA review process with schedule to be determined.		S. Fino

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
04/04/00	27	179	Meeting Request	IDEC to FDA	A. Wei requests two-hour meeting (Type B) with CBER to discuss upcoming BLA. Specific topics are listed.		S. Fino
04/04/00	27		Telecon Minutes	IDEC to file	A. Wei documents her conversation with G. Mills, FDA, regarding an emergency use filing (Serial No. 177) and IDEC's request for Fast Track status for Zevalin. Dr. Mills expressed support on both counts.		
04/03/00	27		Telecon	FDA to IDEC	G. Mills (FDA) requests additional info for Fast Track evaluation. He suggests an amendment to Fast Track submission containing this info. He also indicated that, in order to get rolling BLA approval, IDEC needs to submit a proposed schedule for submission of sections in the pre-BLA meeting package.		
03/31/00	27		Facsimile	IDEC to FDA	A. Wei faxes to John Eltermann (CBER) preparatory materials for a teleconference between CBER and IDEC scheduled for the week of April 3.		
03/30/00	27	178	Info Amend	IDEC to FDA	A. Wei submits Info Amendment: Chemistry regarding a letter of authorization allowing IDEC Pharmaceuticals to cross reference a Type I Master File submitted by Catalytica.		B. Hilal
03/28/00	27		Email	IDEC to IDEC	S. Fino emails Alice Wei to notify her of a conversation with M. Noska (FDA) regarding emergency use telecon 1/28/00.		
03/24/00	27		Voicemail	FDA to IDEC	G. Mills leave message with A. Wei stating his confusion over the setup of an emergency use under Craig Moskowitz at Memorial Sloan-Kettering. Mills requests a call back and an explanation of the emergency use arrangement because FDA doesn't "have any notes for it." Mills suspects FDA clerical error.		
03/24/00	27		Telecon Minutes	IDEC to IDEC	S. Fino documents 1/28/00 telecon between IDEC and G. Mills (CBER) to discuss an Emergency Use Request to treat a patient with IDEC-Y2B8. Minutes of the telecon enclosed. Filed under 1/28/00.		
03/22/00	27	177	Emergency Use Protocol	IDEC to FDA	A. Wei submits a protocol and case report forms outlining the emergency use treatment with Y2B8 for a single patient with intermediate grade B-cell NHL and clinical site documentation.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
03/20/00	27		Voicemail	FDA to IDEC	Jeff Siegel left voicemail for A. Wei requesting a call back.		
03/15/00	26	176	IND Safety Report	IDEC to FDA	A. Wei submits IND Safety Report follow up report of March 1, 2000 for patient 106-04-001 (Initials – LDK). Mfr. Report number is AE 4850-16. Included are copies of the MDS articles cited in the letter to all Y2B8 investigators. IDEC requests the product be identified by the trademark and generic names of Zevalin ™ (ibritumomab tiuxetan).		S. Fino
03/01/00	26	175	Pro. Amend.: C.I.P.	IDEC to FDA	A. Wei submits a protocol amendment consisting of a change in protocol for open-label Protocol 106-98. It is being amended to collect pharmacokinetic samples from selected patients.		S. Fino
03/01/00	26	174	IND Safety Report	IDEC to FDA	A. Wei submits an initial written IND safety report for patient 106-04-001-252 (initials LDK). Report also went via fax because of unexpected fatality and Y2B8 cannot be ruled out. Adverse Event Mfr. Report Number 4850-16.		S. Fino
02/29/00	26		Facsimile	IDEC to FDA	A. Wei sent G. Mills/Medical Reviewer a 7-page fax of an IND Safety Report for patient 106-04-252 (LDK). There was an unexpected fatality and Y2B8 cannot be ruled out. Submission #174 to follow. Adverse Event Mfr. Report Number 4850-16.		
02/24/00	26	173	Pro. Amend.: New Investigator Clinical Info Amended	IDEC to FDA	S. Fino for A. Wei submits a protocol amendment consisting of the addition of three new investigators for Phase II 106-98 and an information amendment consisting of clinical documentation for three investigators for 106-98.		S. Fino
02/22/00	26	172	Information Amendment: CMC	IDEC to FDA	L. Shelly for A. Wei submits an information amendment stating IDEC plans to submit a BLA for Yttrium Y-90. This amendment outlines our proposed strategy for filing information from our contract manufacturer Catalytica, within our licensing application. Catalytica filed a Type I Drug Master File on 10/28/99.		B. Hilal
02/14/00	26	171	Pro. Amend.: New Investigator	IDEC to FDA	A. Wei submits a protocol amendment consisting of 3 new investigators for the open label protocol 106-98. Documentation enclosed.		S. Fino

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
02/09/00	26	170	Info Amend	IDEC to FDA	A. Wei submits a clinical information amendment regarding a brief interruption of IRB approval of IDEC-Y2B8 protocols at Dr. Michael Katin's site (Fort Myers, FL).		S. Fino
02/01/00	26	169	Pro. Amend.: New Investigator	IDEC to FDA	A. Wei submits new investigator information for open label protocol 106-98. Regulatory documents are enclosed for two new investigators		S. Fino
02/01/00	26		Memo of Telecon	IDEC to IDEC	Minutes of telecon held between IDEC and FDA regarding Dec. 22, 1999 Info. Amendment containing an updated proposal for demonstrating comparability between Amersham and Nordion Y-90.		
02/01/00	26		Facsimile	IDEC to FDA	L. Shelly sent M. Noska a list of attendees for the telecon on 2/1/00. L. Shelly asked for the phone number. We call at 11:00 am PST.		
01/28/00	26		Telecon	IDEC to IDEC	Minutes of 1/28/00 telecon between IDEC and CBER to discuss an Emergency Use Request to treat a patient with IDEC-Y2B8. Patient is high risk and not eligible for open label protocol 106-98. G. Mills agrees under certain conditions listed.		
01/28/00	26		Voicemail	FDA to IDEC	George Mills calls A. Wei and says that he anticipates talking at 8:00 PST on 2/2/00.		
01/28/00			Telecon	IDEC to FDA	Telecon occurred between IDEC and FDA regarding Emergency Use. Of Y2B8 for one patient. Minutes filed here.		
01/26/00	25	168	Cross Reference	IDEC to FDA	A. Wei submits a correction to Sr. #160. This version includes two co-principal investigators:		B. Hilal
01/26/00	25	167	Cross Reference	IDEC to FDA	A. Wei submits a correction to Sr. #161. This version includes two co-principal investigators:		B. Hilal
01/21/00	25		Voicemail	FDA to IDEC	D. Green (FDA) leaves message for A. Wei calling in regards to IND 4850 and "change of yttrium for the clinical for the NDA" and pharmacokinetics procedures. He intends to call again.		
01/17/00	25	166	New Investigators	IDEC to FDA	A. Wei submits two new investigators to Protocol 106-98:.		S. Fino
01/12/00	25	165	PICL	IDEC to FDA	A. Wei sends J. Siegel submits a protocol amendment for Protocol 106-98.		S. Fino

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
01/06/00			Document	IDEC	Schering Briefing Document (Zevalin) and associated attachments. Filed in Schering AG binder.		
01/04/00	25		Pre-BLA Meeting Minutes	IDEC	Receipt of FDA minutes from Phase III meeting held on 11/16/99. Purpose of meeting: Discussed dosimetry data and a proposed pharmacokinetic comparability study. Requested by FDA as a result of change in the Y90 supplier from Amersham to Nordion. FDA conclusions are listed.		
12/22/99		164	Information Amendment	IDEC to FDA	A. Wei submits amendment containing proposed studies to demonstrate comparability of Yttrium-90 from Amersham and MDS Nordion.		S. Fino
12/21/99		163	PICL	IDEC to FDA	A. Wei submits protocol amendments to J. Siegel: IRB approvals for changes in protcol for six sites for Ph. III 106-04; IRB approvals for changes in protcol four sites for PH. III Protocol 106-06; changes in Form 1572 for eleven sites for Ph. III Protocol 106-06.		S. Fino
12/21/99		162			A. Wei submits protocol amendment for 106-98 including new investigator. Submission additionally restates that IDEC has special exemption to treat a single patient under Dr. Flinn.		S. Fino
12/16/99	24		Voicemail	FDA to IDEC	M. Noska leaves message for S. Fino regarding two skipped numbers in submission serial number series. Noska indicates that there is no problem with the number gap and no further action is necessary.		
12/16/99	24	161	Letter of Cross Reference	IDEC to FDA	A. Wei submits a cross reference letter authorizing access to the IND. Authorization is provided – A phase I Trial combining IDEC-Y2B8 and High-Dose Beam Chemotherapy with Hematopoietic Progentior Cell Transplant in Patients with Relapsed or Refractory B-Cell NHL.. Investigator **Jane N. Winter**, M.D. Northwestern University Medical School, Chicago, IL		S. Fino

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
12/16/99	24	160	Letter of Cross Reference	IDEC to FDA	A. Wei submits a cross reference letter authorizing access to the IND. Authorization is provided - A Phase I/II Trial of Escalating Dose of Yttrium-90 Labeled Anti-CD20 Monoclonal Antibody in Combination with High Etoposdie and Cyclophosphamide Followed by Autologous Stem Cell Transplantation for Patients with Relapsed B NHL. Investigator **Auayporn Nademanee**, M.D. City of Hope National Medical Center, Duarte, CA		S. Fino
12/16/99	24		Letter	FDA to IDEC	M. Noska sent letter referring to the IND Application and to a meeting held on November 16, 1999 between IDEC and the Agency. A copy of memo is attached. – for Phase 3 to discuss dosimetry data and a proposed pharmacokinetic comparability study.		
12/14/99	24	159	Protocol Amend. New Investigator	IDEC to FDA	A. Wei submits a protocol amendment consisting of new amendment consisting of new investigator information for the open-label protocol 106-98. New investigator **Mansoor Saleh**, Univ. of Alabama, Birmingham, AL		S. Fino
12/13/99			Regulatory Filing	IDEC to IDEC Re: FDA	A. Wei requests filing of document: "FDA requested that lesion measurement information be provided to FDA in an electronic table format (excel) illustrated in the attached table." **Filed with 10/28/99 FDA meeting packet,** as requested.		
12/08/99	24		Letter	FDA to IDEC	Michael Noska sent letter to A. Wei referring to the IND Application and noting a copy of the memorandum from the meeting is attached.		
11/29/99	24	158	Protocol Amendment C.I.P.	IDEC to FDA	A. Wei submits a protocol amendment consisting of a change in protocol for the open-label protocol 106-98 (Amendment #1) The purposes for Amendment #1 are shown.		S. Fino
11/17/99		156& 157			These serial numbers were inadvertently skipped and are now retired		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
11/16/99	24		Meeting agenda/minute	IDEC to IDEC	L. Shelly and A. Wei submit to Regulatory Files the Meeting Announcement, Meeting Attendance, Meeting Agenda, and Meeting Minutes for the meeting with FDA on Nov 16, 1999, a discussion of clinical issues associated with IDEC's prposed licensing application for Y2B8. Topics: 1) clinical overview and update 2) dosimety data 3) the FDA proposed pK study to demonstrate equivalence between yttrium from two vendors.		
11/15/99	24		Facsimile of Attendees	IDEC to FDA	C. Palahang sent fax of the proposed attendees to Mike Noska regarding the FDA Clinical Mtg.		
11/10/99	24		Telecon Minutes	IDEC to IDEC	L. Shelley has conversation with Dr. Green (FDA) to discuss pharmacokinetic study proposed to show equivalence of Yttrium-90 from Amersham and and Nordion.		
11/08/99	24		Facsimile of a Meeting Announcement	FDA to IDEC	Mike Noska sent fax to L. Shelly regarding a meeting announcement for Phase III – for Imaging and treatment of B cell non Hodgkin's lymphoma to discuss dosimetry data and proposed PK comparability study. – date: November 16, 1999 at 9:00 am – 10:30 am in Conference Room 200S WOC1.		
11/04/99	23	155	Info. Amend: Clinical	IDEC to FDA	S. Fino for A. Wei submits an information amendment consisting of an abstract submission. The abstract, "Interim Results From a Phase II Trial of Reduced-Dose Zevalin Radioimmunotherapy for Relapsed or Refractory B-Cell NHL Patients With Pre-Existing Thrombocytopenia: Dosimetry Does Not Predict Hematological Toxicity" has been submitted to the International Conference on Advances in Cancer Immunotherapy.		S. Fino
11/03/99	23	154	Prot. Amend. C.I.P. Changes to Form 1572	IDEC to FDA	A. Wei submits IRB approvals for changes to protocol for 7 sites for Phase III Protocol 106-06 and Changes to Form FDA 1572 for 2 sites to Protocol 106-06. See Study Drug Log on Server.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
11/01/99	23	153	General Corresp. Clinical Meeting Materials	IDEC to FDA	A. Wei submits a Clinical Meeting Material packet and a confirmation of an in-person meeting between CBER and IDEC scheduled for Tuesday, November 16, 1999 from 1:00 to 2:30 pm. Enclosed are 8 copies of the materials and slides are also enclosed and will be updated with interim patient data prior to the meeting. We request the use of a slide projector.		S. Fino
10/29/99	23		Voicemail	FDA to IDEC	G. Mills left voicemail for A. Wei following up to the meeting. He needs to talk to Alice about several issues arising from the meeting. He would try to beep Alice.		
10/28/99	23		Memo of a FDA Meeting	IDEC, Nordion, Schering FDA	Representatives from IDEC, MDS Nordion and Schering AG met with FDA to discuss the change of yttrium-90 (Y-90) suppliers from Amersham to MDS Nordion for future commercial and clinical supply. Topics discussed: **1)** Product Overview **2)** Manufacturing Process and Sources of Y-90 Chloride Solution **3)** Proposed Comparability Studies of Y-90 Chloride Solution from Amersham and MDS Nordion and **4)** Proposed Filing Strategy for the MDS Nordion Y-90 NDA. The major points from the meeting are listed. – Slides follow.		
10/22/99	23		Voicemail	FDA to IDEC	M. Noska left voicemail for A. Wei following up on discussions she had with G. Mills regarding the shift in emphasis of the proposed clinical meeting which was going to be a pre-BLA meeting. Request to resubmit our meeting request to reflect the shift in emphasis on the agenda to include the items which were discussed including dosimetry and any presentation of data.		
10/22/99	23	152	General Correspondence Clinical Meeting Materials	IDEC to FDA	A. Wei sent letter to Jay Siegel confirming a clinical meeting (Type C) with CBER scheduled to occur 11/16/99. During the meeting IDEC is to provide an update on the clinical development of Y2B8 for the treatment of patients with relapsed or refractory low grade, follicular or transformed CD20+ B cell NHL and Rituximab-refractory follicular NHL. Agenda and list of planned attendees enclosed.		S. Fino

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
10/18/99	23		Letter	IDEC to FDA Ethics	A. Wei submits a letter to Ms. Jenny Slaughter, Acting Group leader FDA Ethics Office stating that IDEC recently employed two former CBER/FDA employees (R.Lizambri and L.Shelly) and that we understand certain restrictions. We listed 3 rules and if clarification is necessary to contact us.		
10/08/99	23		Telecon Draft Confidential	IDEC Internal	Confidential Telecon Minutes from L. Shelly regarding the telecon with M. Fauntleroy, D. Kim and L.Shelly – Electronic Filing of CT Scans and Nuclear Medicine Images to the BLA.		
10/07/99	23		Telecon	IDEC to FDA	L. Shelly, B. Hilal, M. Thompson phoned Daniel Kearns at FDA/CBER to discuss IDEC's proposal to make a claim for categorical exclusion from an environmental assessment. IDEC plans to submit a BLA on 6/30/2000 for marketing approval of IDEC-Y2B8. IDEC presented information on submitting the BLA, who manufactures, IDEC ships the drug substance to a contract manufacturer Catalytica in NC and the mfg two other components – these components are shipped as a kit to a clinical site where the antibody is readiolabeled with Y-90 and lastly both companies intend to maintain compliance with regulations.		
10/04/99	23		Telecon Draft Confidential	IDEC Internal	Confidential Telecon Minutes from L. Shelly regarding the telecon with George Mills, Christine White and Leslie Shelly – FDA Request for information on the pre-BLA Clinical Meeting on 11/16/99.		
09/30/99	23	151	Protocol Amendment	IDEC to FDA	A. Wei submits protocol amendment adding new investigator for Phase III Protocol 106-06.		S. Fino
09/27/99	23		Letter	FDA to IDEC	M. Noska sends A. Wei minutes of telecon b/w IDEC and FDA on August 13, 1999. Telecon held to obtain clarification on comments made by FDA in letter of June 2. Also discussed: developmental goals for Phase 3 protocol.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
09/24/99	23		Fax	FDA to IDEC	Fax from E. McFadden/ M. Noska to A. Wei containing Pre-BLA Meeting Announcement; meeting to "discuss clinical aspects of proposed BLA submission including labeling indication, clinical data, dosimetry and safety updates." Stipulates that meeting package must be received 4 weeks prior to meeting.		
09/23/99	23	150	Letter	IDEC to FDA	Letter to FDA regarding protocol 106-98. Bryan Leigh named as project coordinator and IDEC contact, replacing C. White. Amendments to Appendices J and K included.		S. Fino
09/21/99	23		Fax	FDA to IDEC	Formal meeting announcement from Michael Noska, FDA, regarding Pre-BLA meeting to "discuss issues related to submission of a NDA for Y-90 from Nordion." Meeting is scheduled for Oct. 28, 1999, from 1pm to 2:30pm in WOC1, Conf. Rm 200S.		
09/21/99	23		Voicemail	FDA to IDEC	Emily McFadden left voicemail for A. Wei stating she is in process of scheduling another meeting for her and need to discuss dates proposed.		
09/13/99	23	149	Meeting Request		Pre-BLA meeting request		S. Fino
09/13/99	23		Voicemail	FDA to IDEC	M. Noska calls Cher asking for some clarification about pre-NDA meeting request.		
09/13/99	23		Phone call	IDEC to FDA	L. Shelly responds to voicemail from M. Noska to A. Wei. Shelly confirmed for Noska that we want face-face meeting, not teleconference, re: changing yttrium suppliers. Noska intends to contact us in a week.		
09/10/99	23	148	CALA Questionnaire	IDEC to CBER	Completion of CBER CALA Questionnaire (the same sent electronically to Michael Fauntleroy on 9/8/99).		S. Fino
09/09/99	23	147	Letter to FDA	IDEC to CBER	Nordion meeting package providing data and requesting a meeting w/ Leon Epps.		
09/07/99	23		Voicemail	FDA to IDEC	G. Mills returns A. Wei's phone call on Aug 27, 1999.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
09/02/99	23	146	Letter response to FDA	IDEC to CBER	S Fino for A. Wei responds to G. Jones and letter of June 2, 1999. Restates findings of August 13, 1999 teleconference with FDA: Protocol 106-06 not to be submitted as separate BLA, rather, a single BLA to be filed based on 106-04 with 106-06 as supportive trial. Telecon agreements regarding 106-06 restated. Four attachments: 1) original response to June 2 letter 2) 90 patient interim analysis for protocol 106-04 3) minutes from telecon 4) abstracts for ASH meeting Dec 1999.		
09/01/99	23	145	Protocol Amend - New Protocol	IDEC to FDA	Open label protocol 106-98		S. Fino
08/25/99	23	144	IND Safety Report	IDEC to FDA	A. Wei submits follow up to safety report for patient in 106-06. Submitted to J. Siegel.		S. Fino
08/17/99	23		Voicemail	CBER to IDEC	M. Noska of CBER calling A. Wei to clarify possible confusion about teleconference location: Teleconference is to take place in conference room and not George Mills office.		
08/13/99	23	143	Prot Amend New Investigator	IDEC to FDA	A. Wei submits a protocol amendment for Phase III protocol 106-04 consisting of one new investigator.		S. Fino
08/12/99	23		Fax	IDEC to FDA	A. Wei faxes 90th Patient Interim Analysis Report for 106-04 for review by George Mills, as requested. Discussion planned for 8/13/99 re: Protocol 106-06.		
08/11/99	23		Response to FDA Request for Info.	IDEC to FDA	A. Wei sent fax of our draft response to the FDA's 6/2/99 letter for protocol 106-06. IDEC will contact G. Mills on 8/12/99 at 11:00 am to discuss the contents of this draft response.0		
08/10/99	23	142	IND Safety Report	IDEC to FDA	A. Wei submits an Initial written report for female 69 year old patient #106-06-01-031(initials RMS) Event of subdural hematoma. Patient found to have a nadir platelet count 25,000. Received platelet transfusions & remains in the hospital.		S. Fino

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
08/04/99	22	141	Prot Amend New Invest C.I.P. Changes to FDA 1572 Form	IDEC to FDA	A. Wei submits a protocol amendment for Phase III consisting of one new investigator for Protocol 106-04.		S. Fino
07/27/99	22	140	Prot Amend.: New Investigator	IDEC to FDA	A. Wei submits a protocol amendment adding one new investigator for Phase II 106-05 and one new investigator to 106-06.		
07/20/99	22		Voicemail	FDA to IDEC	Emily McFadden left voicemail confirming meeting date for teleconference of August 13, 1999 from 1:00 - 2:00pm.		
07/20/99	22		Facsimile	FDA to IDEC	Michael Noska announces Telecon date of August 13, 1999 from 1:00-2:00 to discuss Y2B8 developmental goals for P3 protocol 106-06 & obtain clarification of FDA comments in 6/2/99 letter. Indication Imaging and treatment of B cell non-Hodgkin's lymphoma.		
07/09/99	22	139	Request for Telecon	IDEC to FDA	S. Fino for A. Wei submits a Request for a Teleconference. IDEC stated we received a letter from FDA dated 6/2/99 referencing Phase III protocol 106-06. During 3/31/99 telecon with FDA we were invited to discuss concerns regarding this letter. We request an expedited telecon to discuss developmental goals, obtain clarification on their comments and considerations for determining the adequacy of a registration trial and present IDEC's clinical strategy for this protocol		S. Fino
07/08/99	22	138	Memo of a Telecon	IDEC to FDA	A. Wei submits a memorandum of a telephone conversation held with M. Fauntleroy with CBER & C. White, P. Chinn, B. Parker, R. Lamb and S. Fino from IDEC to discuss the dosing of a patient under Protocol 106-04. Mr. Fauntleroy requested that the telecon of 8/11/98 be documented and formally submitted to the IND. Enclosed are the minutes of the telecon.		S. Fino

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
07/06/99	22		Mass Mailer	FDA to IDEC	Jane Henney, Commissioner sent letter to [Dear President/CEO/Blood Establishment Director:] The purpose of this letter is to request your assistance in assuring the Agency and the public that your firm has addressed the year 2000 (Y2K) problem as it affects the adequate supply of safe and effective biological products. The Y2K problem can cause a variety of errors in how dates are expressed or computed that could adversely affect automated process controls and clinical and non-clinical data integrity. Requested to complete the attached survey concerning the status of actions taken to address the year 2000 problem, documentation regarding the steps taken to prepare for the year 2000 and should be available for FDA review during inspections.		
06/24/99	22	137	Protocol Amend: New Investigators C.I.P.	IDEC to FDA	A. Wei submits Protocol Amendments consisting of IRB approvals /C.I.P. two sites 106-04; and four sites for 106-06.		B. Powell
06/24/99	22		Voicemail	FDA to IDEC	G. Mills left voicemail for A. Wei returning her call noting that she surely would want to have a teleconference. In structure at FDA post-FDAMA, create letter/IND amendment with focus and our alternative.		
06/23/99			Voicemail	IDEC to FDA	A. Wei leaves message on George Mills voicemail indicating that we had received letter sent by FDA on 6/2/99 regarding Protocol 106-06. She also mentions we would like to proceed with having a telecon with George and any other relevant parties to discuss the letter.		
06/10/99	22	136	IND Safety Report	IDEC to FDA	A. Wei submits an Initial Written Report for patient number 106-06-11-019. The patient is a 53 yr. old male with malignant lymphoma. The patient was admitted to the hospital on May 5i99 for deep vein thrombophlebitis. There was no change in the patient's performance status. 4850-14		S. Fino
06/02/99	22		Letter	HHS to FDA	G. Jones to A. Wei		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
05/28/99	22		Letter	Info Systems Scotland to IDEC	Lisa M. Anderson ñ Drug Information Specialist (National Health Service in Scotland) sent letter enclosing a leaflet that explains in detail the background to the following. Letter states she is aware from Scrip that ibritumomab tiuxetan is currently in Phase III trials for low-grade and/or follicular non-Hodgkin's B-cell lymphoma and do we intend to license this product in the UK if so to forward information.		
05/24/99	22	135	General Correspondence. Request for Pre-NDA meeting CMC	IDEC to FDA	A. Wei sent letter requesting a 90-minute meeting with CBER personnel to discuss CMC topics related to a NDA associated with our planned BLA. These CNC topics affect our IDEC product Ibritumomab tiuxetan (Y2B8) under clinical investigation. IDEC also would like to discuss role of Indium-In-111.		
05/18/99	22	134	Protocol Amend: CIP/New Investigator, Change in FDA 1572	IDEC to FDA	A. Wei submits **1)** A prot. amend. for a change in protocol for six sites for the Phase III Protocol 106-04. **2)** A prot. amend adding a new investigator, IRB approvals for a change in protocol and a change in Form FDA 1572 for four sites for the Phase II Protocol 106-05 and **3)** A Prot. Amend. consisting of a change in protocol (Amend 3) and IRB approvals for a change in protocol for five sites for the Phase III Protocol 106-06.		S. Fino
04/23/99	22		Voicemail	FDA to IDEC	G. Mills called and left a voicemail stating that he has talked to a statistician and talked in following a conversation in terms of the statistical method for our proposed phase III trial. He asked that Alice give him call.		
04/23/99	22		Voicemail	FDA to IDEC	Leon Epps called and left A. Wei a voicemail stating that she could leave him a message the next time she called in terms of what issues you need him to address or some guidance on whatever the issue is.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
04/20/99	22		Letter	FDA to IDEC	S. Sickafuse sent letter referring to IND Application for Ibritumomab tiuxetan [Indium-In-111 Radiolabeled and Yttrium-Y-90 Radiolabeled Murine Monoclonal Antibody (2B8-MX-DTPA) to CD20]; Bone Marrow and G-CSF and to the meeting held on 3/23/99. Attached is a Memo of the Overview of the pre BLA CMC. **Not in file.**		
04/17/99	22		Voicemail	FDA to IDEC	G. Mills called again trying to catch up with Alice about the Yittrium. **Not in file.**		
04/16/99	21	133	Protocol: New Invest./CIP/Info: Clinical	IDEC to FDA	A. Wei submits an Information and Protocol Amend enclosing the following: **1)** a clinical info amend consisting of IRB approval documents for the Phase III Protocol 106-04; **2)** a clinical info consisting of IRB approval documents for the Phase II Protocol 106-05 ; and **3)** a protocol amend adding two new investigators		
04/16/99	22		Voicemail	FDA to IDEC	G. Mills called and left a voicemail for A. Wei to talk about the Yittrium source that we are using in our trials. **Not in file.**		
04/15/99	21	132	Annual Report	IDEC to FDA	A. Wei submits 1998-99 Annual Report containing 8 abstracts and updated stability data. All portions of 106-03 clinical study are being conducted by Pharmaceutical Research Associates, INC including site monitoring, SAE reporting to the sponsor, data management , and report writing. For Protocol 106-04, IBAH will conduct Good Clinical Practices audits and independent contract clinical monitors will conduct site visits under the direction and management of IDEC personnel.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
04/13/99	21		Pre BLA CMC Meeting Memorandum	FDA to IDEC	S. Sickafuse sent memo regarding the 3/23/99 pre BLA CMC meeting with IDEC regarding the 111In and 90Y Radiolabeled Murine Monoclonal Antibody (2B8-MXóDTPA) to CD20: IND 4850. Memo states IDEC plans for 2 BLA's for the product. 1st BLA for treatment of patients with follicular B-Cell non-Hodgkin's lymphoma who are refractory to chemo and Rituximab ñ anticipated spring of 2000. 2nd BLA for treatment of patients with relapsed or refractory low grade or follicular and transformed B-cell non-Hodgkin's lymphoma for late fall of 2000. Memo reviews submission contents, Characterization, Manufacturing, use of Gentamicin in Bioreactor Medium, Radiolabeling Kit, Comparability Studies, Stability Data.		
04/05/99	21	131	Protocol Amendment New Investigator, Change in Protocol	IDEC to FDA	S. Fino for A. Wei submits **1)** a clinical info. amend. for one site for the Phase II protocol 106-03; **2)** a prot. Amend. consisting of a change in sub-investigators and a change in protocol for the phase III protocol 106-04 and **3)** adding a new investigator and a change in protocol for the phase II protocol 106-05 **4)** adding three new investigators and a clinical info amend. for two sites for the Phase III protocol 106-06.		S. Fino
04/01/99	22		Voicemail	FDA to IDEC	Mike Nostan called A. Wei regarding question about submitting an NDA along with a BLA. Please give a call at your earliest convenience 301-827-6953. **Not in file.**		
03/29/99	21	130	Response to FDA Request for Information	IDEC to FDA	C. Palahang for A. Wei sent letter regarding a 2/25/99 telecon between G. Mills/Medical Reviewer and IDEC Pharm: C. White, D. Shen and A. Wei to discuss protocol 106-06. Enclosed is the information requested regarding the design of 106-06 also our rationale for selection of target ORR of 35% and product administration information from Appendix I of the protocol.		C. Palahang

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
03/29/99	21		Voicemail	FDA to IDEC	George Mills called A. Wei to follow-up after a meeting and has a number of discussion points to catch up on. He stated that they will be sending a letter in following up onto in terms of design issues and that they are going to require the performance of the indium study in order to document the dosimetry. G. Mills called A. Wei to follow-up after a meeting and has a number of discussion points to catch up on. He stated that they will be sending a letter in following up onto in terms of design issues and that they are going to require the performance of the indium study in order to document the dosimetry.		
03/25/99	21	129	Protocol Amend. C.I.P. ñ New Investigators	IDEC to FDA	A. Wei submits a protocol amendment consisting of a change in Protocol 106-06 and protocol amendment consisting of the addition of 2 new investigators for 106-06.		
03/25/99	21		FAX Response to FDA Request for Information	IDEC to FDA	S. Fino for A. Wei sent a Response to FDA for Information (George Mills) regarding the design of Protocol 106-06. Enclosed is our rationale for the selection of the target ORR of 35% and product administration information from Appendix I of the protocol. **The fax confirmation sheet was misplaced.**		
03/23/99	21		Voicemail	FDA to IDEC	G. Mills left voicemail for A. Wei stating he had talked to the statistician and talked following conversation in terms of the statistical modeling for the proposed Phase III trial. He requested a call back to catch up on their progress/opinions as of now. Looks like additional work and some structuring.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
03/23/99	21		Memo	IDEC	IDEC held a pre-BLA CMC meeting with FDA to discuss upcoming CMC section of the ibritumomab tiuxetan (IDEC-2B8) license application. The specific topics were discussed: 1) the filing strategy for the IDEC C2B8 license application 2) the proposed commercial manufacturing scheme with minor process changes 3) the use of CD20 binding assay by competitive inhibition for assessing potency 4) proposed comparability testing for IDEC-2B8-MX-DTPA 5) the proposed stability program and plan for assigning expiration dating.		
03/16/99	21	128	Other: Designation of a Proprietary & Established Name	IDEC to FDA	A. Wei submits a Designation of a Proprietary and Established Name for IDEC-2B8-MX-DTPA. Brand Name: Zevalin. We hereby notify the agency of the assignment of an established name from USAN: ibritumomab tiuxetan.		
03/05/99	21		Electronic Submission	IDEC to FDA	A. Wei sends a disk containing the electronically formatted documents for Protocol 106-06 Amend. #2 including appendices. Also an electronic copy of the letter providing response to FDA's request for information regarding 106-06 Amend. #2 and the associated case report forms. Documents are formatted in Windows 95, Word 6.0.		
03/02/99	20		Telecon	FDA to IDEC	G. Mills called C. Palahang and requested a document that A. Wei is working on be sent to him on a disk along with the 12/22/98 revised protocol submission. This would allow him to incorporate the document.		
03/02/99	20	127	Response to FDA Request for Information: Protocol 106-06	IDEC to FDA	A. Wei submits a Response to FDA for Information regarding protocol 106-06, phase II and III. Included in the letter is IDEC's reasoning for 1) elimination of indium use in this trial, 2) documentation of patient's prior response, and 3) confirmation of the target duration of response.		S. Fino

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
03/02/99	21		Facsimile	IDEC to FDA	A. Wei sent fax to G. Mills @ CBER in response to FDA Request for Information ñ Protocol 106-06 ñ Cover sheet state on 2/8/99 a telecon was held between G. Mills @ CBER and C. White & A. Wei to discuss 106-06. As requested IDEC provided our reasoning for elimination of indium use in this trial -- documentation of patient's prior response ñ and confirmation of the target duration of response.		
02/26/99	20	126	IND Safety Report	IDEC to FDA	A. Wei submits an initial written IND Safety Report for patient number 106-05-013 67-year old female with B-cell non-Hodgkin's lymphoma (initials MMS). Event involving thrombocytopenia 12/16/98. It was not initially determined to be reportable. The event was expected, however, information received 2/11/99 re: prolonged myelosuppression, now is determined to be reportable. AE 4850-013		S. Fino
02/23/99	20	125	General Req. for Pre-BLA CMC	IDEC to FDA	A. Wei submits a request for Pre-BLA Meeting - CMC confirming with CBER and IDEC for March 23, 1999 from 1-3pm. The meeting is in reference to our planned BLA. We sent 8 copies including agenda, goals, and information on the content for the CMC section and a list of proposed attendees.		
02/19/99	20	124	Info. Amend: Clinical	IDEC to FDA	A. Wei submits four recent abstract submissions. The first two were submitted to the 35th Annual Meeting of the American Society of Clinical Oncology Atlanta, GA ñ The third abstract submitted to Lugano, Switzerland and the fourth abstract to the Society of Nuclear Medicine 46th Annual Meeting, Los Angeles, CA.		S. Fino
02/17/99	20		Voicemail RE: Binding	FDA to IDEC	Dr. Mark Brunswick called A. Wei about the recent amendment 4850 with the results of the testing on the lot that failed. And that the binding does not need to be done anymore.		
02/08/99	20		Facsimile	FDA to IDEC	Emily McFadden sent fax from S. Sickafuse regarding the Pre-BLA Meeting Announcement set for March 23rd from 1:00-3:00ñ Indication: Imaging and treatment of B-Cell non-Hodgkin's lymphoma.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
02/08/99	20		Voicemail	FDA to IDEC	S. Sickafuse called A. Wei to announce the time of the CMC pre-Bla meeting for Tuesday March 23rd from 1 to 3. She will need our meeting packages by 2/23/99.		
02/05/99	20	123	CMC Request for Information	IDEC to FDA	A. Wei submits a CMC response to request for information on a dose prep failure noted in Serial No. 113.		
02/03/99	20	122	Info Amend: Clinical Protocol Amend.: CIP	IDEC to FDA	A. Wei submits a clinical info amendment with signed protocols for amendments 2 & 3 & IRB approval information for Phase III 106-04; also a clinical info amendment for Phase II 106-05.		
01/28/99	20	121	Prot. 10Amend: C.I.P. / New Investigator	IDEC to FDA	A. Wei submits a Protocol Amendment consisting of the addition of one new investigator & a change in Protocol for 106-04. Also an amendment consisting of the addition of one new investigator, and Change in Protocol for 106-06.		S. Fino
01/26/99	20	120	Info Amendment Clinical Prot. Amend. New Invest./ C.I.P. Change in Invest	IDEC to FDA	A. Wei submits a clinical info. amendment for Phase II protocol 106-03; and Phase III protocol 106-04 changes in subinvestigators & change in protocol (amendment #3); and a protocol amendment for adding 2 new investigators for Phase III protocol 106-06 (really only one) **Hani Nabi**, State Univ. of New York, Buffalo Sisters of Charity Hosp., Buffalo, NY .		S. Fino
01/22/99	19	119	General Correspondence	IDEC to FDA	A. Wei submits a letter of General Correspondence to request a Pre-BLA Meeting- CMC. A request for a 90-minute meeting with CBER to discuss CMC topics related to our planned Biologics License application. These topics affect IDEC's Products Indium-In-111 Radiolabeled Murine Monoclonal and Yttrium-Y-90 Radiolabeled Murine Monoclonal to CD20.		S. Fino
01/12/99	19		Facsimile	CBER to IDEC	S. Sickafuse sent fax to A. Wei ñ Message Meeting summary for Nov. 17, 1998 pre phase 3 meeting regarding IND 4850. Attached is a memorandum with an intro: stating IDEC has 2 Phase 3 protocols for the product also the discussion section re: the reviewers concerns.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
01/11/99	19		FDA Telecon	IDEC to CBER	A. Wei telephoned M. Brunswick, Ph.D., CBER to discuss (1) the proposed elimination of the binding kit, (2) the BLA for IDEC-Y2B8, and (3) conversion of Torreyana to a multi-product campaign basis facility.		
01/08/99	19	118	Prot. Amend New Investigator	IDEC to FDA	A. Wei submits a protocol amendment consisting of 4 new investigators for the Phase II Protocol 106-05 & new investigators for the phase III protocol 106-06.		S. Fino
12/29/98	19	117	Prot. Amend New Investigator	IDEC to FDA	A. Wei submits a protocol amendment consisting of the addition of new investigator for Phase II Protocol 106-05.		S. Fino
12/23/98	19	116	Prot. Amend. New Investigator	IDEC to FDA	A Wei submits a protocol amendment consisting of the addition of a new investigator for the Phase II Protocol 106-05.		S. Fino
12/22/98	19	115	Response to FDA Request for Information	IDEC to FDA	A Wei submits letter stating that on November 17, 1998 a pre-Phase III meeting was held between CBER and IDEC to discuss protocol 106-06 and accelerated approval mechanisms. IDEC requests that accelerated approval be applied to Indium-In-111 Radiolabeled Murine Monoclonal (2B8-MX-DTPA) and Yttrium-Y-90 Radiolabeled Murine Monoclonal (2B8-MX-DTPA) to CD20. Enclosed is the revised protocol Appendix 1 (Amend #2).		
12/22/98	19		Fax	IDEC to FDA	A. Wei sent a 6-page fax to Mike Noska at CBER regarding submission #115.		
12/22/98	19		FACSIMILE SUBMISSION, Response to FDA request for information	IDEC to FDA	A. Wei sent a 131-page fax to George Mills at CBER regarding submission #115.		
12/17/98	19	114	Prot. Amend. Change in Protocol, New Investigator	IDEC to FDA	A Wei submits protocol amendment consisting of the addition of one new investigator for Phase II Protocol 106-05 **Dr. Mansoor Saleh**, Univ. of Alabama Birmingham, Comprehensive Cancer Center, Birmingham, AL. Site 106-05-33.		S. Fino

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
12/16/98	19	113	Information Amendment: CMC	IDEC to FDA	A. Wei enclosed documentation supporting our proposal for removal of a binding assay from ongoing clinical trials and future commercial distribution.		
12/09/98	17	112	Prot. Amend.: Change in Protocol, New Investigator	IDEC to FDA	A. Wei submits a protocol amendment 2 new investigators and change in protocol for Amendment #1 for Phase III protocol 106-06.		S. Fino
12/04/98	17	111	Prot. Amend.: New Investigator	IDEC to FDA	A. Wei submits a protocol amendment consisting of the addition of new investigator.		S. Fino
12/02/98	17	110	Prot. Amend.: New Investigator	IDEC to FDA	A. Wei submits a protocol amendment consisting of the addition of 2 new investigators.		S. Fino
11/23/98	17	109	Prot. Amend. New Invest. Info. Amend. Clinical	IDEC to FDA	A. Wei submits protocol amendment consisting of 2 new investigators for Phase II protocol 106-06 and clinical info amendment consisting of revised informed consent document and IRB approval.		S. Fino
11/10/98	17		Voicemail	FDA to IDEC	G. Mills left voicemails for A. Wei, stating he has a list of items from a discussion for input. Called again later with phone numbers and times to contact him, also states heís got good input in terms of planning.		
11/05/98	17	108	Information Amendment: CMC Cross Reference Letter	IDEC to FDA	A. Wei submits a letter of cross-reference authorizing the FDA access to two Nycomed Amersham Drug Master Files: DMF #3743 for Indium (In-111) Chloride **and** DMF #8810 for Yttrium (Y-90) Chloride. These DMF's support BB-IND 4850.		
11/02/98	17	107	Prot. Amend. New Invest & CIP Info Amend. Clinical	IDEC to FDA	A. Wei submits protocol amendment Phase III Protocol 106-04 one new investigator and two new investigators for Phase II Protocol 106-06 and a C.I.P. (Amend#1) for Phase II Protocol 106-05.		S. Fino

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
10/22/98	17	106	General Correspondence: Supplemental Meeting. Materials	IDEC to FDA	S. Fino for A. Wei sent letter to confirm an in-person meeting between CDER and IDEC scheduled for Nov. 17, 1998 3:00 to 4:30 pm to discuss a Phase III trial design. Sharon Sickafuse requested 8 copies of an executive summary. Will contact Ms. Sickafuse 2 weeks before the meeting to confirm the location.		S. Fino
10/15/98	17	105	Prot. Amend. New Invest. & C.I.P. Info. Amend.: Clinical	IDEC to FDA	A. Wei submits a protocol amendment consisting of one new investigator for Phase III 106-04 and one new investigator for Phase II 106-06 a protocol amendment C.I.P. for 3 investigators 106-04 and one investigator for Phase II 106-05 and a clinical information amendment consisting of supplemental clinical documentation for one investigator for 106-06.		S. Fino
10/03/98	17		Voicemail	FDA to IDEC	S. Sickafuse left voicemail for A. Wei regarding the IND and the pre Phase III meeting request or telecon request. All can make the 11/17/98 date at 3:00 ñ 4:30pm or 11/24 date at 3:00 ñ 4:30pm. IDEC may choose date.		
09/29/98	17		Voicemail	FDA to IDEC	S. Sickafuse left voicemail with phone and informed A. Wei she would be the point of contact for IND 4850 while M. Fauntleroy is on four month detail and she received the meeting request/ Possible dates 11/17th or 11/24th . She also requested sending a summary of protocol 106-03 (requested 8 copies as an amendment to the IND for P. Keegan and Karen Weiss that obviously aren't going to go through the 7 Volumes of the summary that was sent with the final report).		
09/24/98	17		Voicemail	FDA to IDEC	S. Sickafuse called A. Wei informing her the IND has been assigned to her while M. Fauntleroy is on detail for 4 months. She received the pre pivotal Submission and was wondering why 12 copies of an 8 Volume submission was sent when only 2 people would be looking at it. A. Wei returned call and explained that it has been required of IDEC in the past, if it contained background information for an FDA meeting, especially pre pivotal mtgs.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
09/23/98	17		Internal Memorandum	Alice W. and S. Fino for Distribute	FDA Imaging Working Group Meeting (IWG): Presentation of Dosimetry Data Results from IDEC Protocol 106-03		
09/22/98	17	104	Letter Authorizing Cross Reference	IDEC to GNE	A. Wei authorizes access to IND 4850. Cross-reference is provided to allow review of manufacturing, non-clinical and clinical info. Re: the testing, release & use of the radiolabeled antibody. Investigator responsible for conduct is: Myron S. Czuczman, Roswell Cancer Institute, Buffalo NY.		
09/22/98	18a 18b 18c 18d	103	General Correspond.: Pre-Pivotal Meeting Materials	IDEC to FDA	A. Wei submits a requests a meeting or telephone discussion with CBER to discuss the design of a second pivotal Phase III clinical trial. We wish to establish and demonstrate more fully the efficacy and safety of our radioimmunotherapy Yttrium-Y-90. We wish to further develop this for the treatment of patients with follicular NHL who have failed all therapies including approved agent Rituxan. **(8 Volumes sent to FDA totaling 44,336 pages).**		S. Fino
09/16/98	17	102	Prot. Amend. : New Investigators	IDEC to FDA	A. Wei submits a protocol amendment consisting of one new investigator for Protocol 106-05, and one new investigator for Protocol 106-06,		S. Fino
09/08/98	17	101	Prot. Amend.: New Investigator Prot. Amend.: Clinical Doc.	IDEC to FDA	A.Wei submits a protocol amendment consisting of the addition of one new investigator for IDEC-Protocol 106-05, and two investigators for IDEC Protocol 106-04,		
09/03/98	17		Electronic Submission CD Rom (Serial #099)	IDEC to FDA	A. Wei sent Michael Fauntleroy a CD ROM containing the electronically formatted document IDEC Protocol 106-05 Amendment #1		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
09/01/98	17		Letter of Authorization	IDEC to James Karr Roswell Cancer Institute	IDEC sent letter to James Karr @ Roswell Park Cancer Institute authorizing Myron S. Czuczman @ RPCI access to IND applications for IDEC-Y2B8 & IDEC/-In2B8. Also currently the FDA has not placed any clinical holds on these applications.		
08/28/98	16a & 16b	100	Imaging Working Group Background Materials	IDEC to FDA	A. Wei submits Dosimetry Report for Protocol 106-03 (including ORISE and Mayo Clinic dosimetry reports) for Imaging Working Group Meeting scheduled for September 23, 1998. (2 Volumes) Added set of Slides to submission packet on 10/06/98.		S. Fino
08/21/98	15	099	Prot. Amend Change in Protocol; New Investigators; Information Amend: Clinical	IDEC to FDA	A. Wei submits a change in Protocol Amendment and new investigator information for (106-05); (106-06) and supplemental documentation for N. Bartlett, WA University (106-05);		
08/20/98	15		Voicemail	FDA to IDEC	George Mills left A. Wei a voicemail stating he was following up for the Imaging Working Group on 9/23/98 at 10 am. It will be at Woodmont 1 Bldg. Conference room. Send 3 copies in for them.		
08/13/98	15	098	Prot. Amend.: New investigators	IDEC to FDA	A. Wei submits a protocol amendment consisting of three new investigators for Protocol 106-05.		S. Fino
08/11/98	15	097	IND Safety Report	IDEC to FDA	Enclosed is a follow up to a written report for patient #106-03-03-203 (initials J-R), 62 yr. old female with Stage IV B-Cell. After initial dose, patient admitted to hospital with massive progression in abdominal area. Patient died 12/2/96. Attached is a copy of the discharge summary.		S. Fino

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IDEC-Y2B8 Zevalin (ibritumomab tiuxetan)

DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
08/11/98	15		Voicemail	FDA to IDEC	M. Fauntleroy left a voicemail stating he got a chance to load up the CD-ROM sent to him July 10th for protocol 106-05. He was happy all appendices did load & were in the appropriate windows format. He was able to view & load. Again the actual protocol 106-05 was not in a translatable format. He requested it be sent again on a floppy. He stated that she did not have to burn a CD-ROM. Please call him on 8/5 or 6. **Document not found in binder.**		
08/06/98	15	096	Protocol Amendment: New Investigator	IDEC to FDA	C. Evans for A. Wei submits a protocol amendment consisting of the addition of a new investigator for the Phase II Protocol 106-05. The IRB approval is an expedited approval for one patient to be entered under this protocol prior to formal IRB review on August 20, 1998.		S. Fino, C.Evans
08/05/98	15		Electronic Diskette	IDEC to FDA	A. Wei sent Michael Fauntleroy per his request a disk containing the electronically formatted document IDEC Protocol 106-05. Formatted in Palatino, and in Windows 95, Word 6.0.		
07/31/98	15	095	Protocol Amendment New Investigator	IDEC to FDA	C. Evans for A. Wei submits a protocol amendment consisting of documentation for new investigator for Phase II Protocol 106-05.		S. Fino, C.Evans
07/20/98	15		Voicemail	FDA to IDEC	M. Fauntleroy left a message for Cher stating that G. Mills would be unavailable to talk to Alice today at 11 EST. Instead if Alice could call M. Fauntleroy's office at that time G. Mills would be present. (included is the same message left on A. Wei's machine)		
07/17/98	15		Telecon	FDA to IDEC	Dr. Brunswick called C. Palahang to inform Alice that he was just reviewing the annual report for phase III of 4850. He asked if he could be updated on the number of patients currently enrolled, this information would help him see how the study was progressing.		

Chronology for BB-IND 4850
IDEC-Y2B8 Zevalin (ibritumomab tiuxetan)

DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
07/15/98	15	094	Protocol Amend. New Investigators Info. Amendment: Clinical	IDEC to FDA	C. Evans for A. Wei submits a protocol amendment consisting of the addition of one new investigator for the Phase III Protocol 106-04 and an information amendment consisting of supplemental clinical documentation for two investigators for Protocol 106-04 and a protocol amendment consisting of the addition of two new investigators for the Phase II protocol 106-05		S. Fino, C.Evans
07/10/98	14	No #	CD ROM	IDEC to FDA	A. Wei submitted a CD ROM containing the electronically formatted documents for IDEC Protocol 106-05, including appendices, and a certification that the CD is free from viruses. **NO SERIAL NUMBER ASSIGNED.**		
07/09/98	14	093	Protocol Amend. New Investigators	IDEC to FDA	A. Wei submits new investigator information for Phase III protocol 106-04.		S. Fino
07/07/98	14		Voicemail	FDA to IDEC	G. Mills said yes to the first item. September 23 is what was marked on his calendar for the Imaging Working Group. Then he mentioned it sounded like everything went fine on the other patient and he was glad we got him treated. He mentioned taking a few more time points since we're evaluating the patient on the follow-up.		
07/06/98	14		Voicemail	FDA to IDEC	G. Mills @ FDA called A. Wei and said he was returning Christine White's & Alice's phone calls and gave his phone number to call again.		
07/05/98	14		Voicemail	FDA to IDEC	M. Fauntleroy left voicemail for Christine White stating when heíd be in the office and that heíd been out a few days. Interested in our single patient exemption. He stated FDAís need for patientís complete history, a copy of the inclusion/exclusion criteria of the ones that we want to violate and an IRB approved informed consent written specifically for this patient with the stipulations clearly stated.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
07/01/98	14		Telecon	IDEC to FDA	AGL, C. White, T. Olejnik, and S. Fino called FDA to discuss a special exemption to treat a patient under the 106-06 protocol. Since Dr. George Mills, Michael Fauntleroy and Dr. Pat Keegan were not available, IDEC participants spoke to Dr. Richard Steffen. Christine White stated we had an urgent request from an investigator to treat a patient with Y2B8 under protocol 106-06. Dr. White reviewed the issues due to his unfamiliarity with the project. He stated he didn't see any real problems and would grant exemption for the patient to be treated with the reduced dose. (0.3mCi/kg).		
07/01/98	14		Letter of Cross Reference	IDEC to Roswell Park Cancer Center	A. Wei sent letter authorizing Myron Czuczman at Roswell Park, Buffalo NY access to IND applications for IDEC-Y2B8 ñ BB-IND 4850 and Rituxan BB-IND 4904. This letter also informs you that FDA has not placed any clinical holds on these applications		
07/01/98	14	092	Protocol Amend. New Investigator FDA Exemption	IDEC to FDA	C. Evans for A. Wei submits a protocol amendment consisting of the addition of one new investigator for the Phase II Protocol 106-06. ID received special exemption, from Dr. Richard Steffen of CBER to treat patient. The patient was randomized to the Rituxan arm of the trial, did not respond, and upon progression of the disease requested treatment with Y2B8 under 106-06 and to receive reduced dose of 0.3 instead of 0.4 dose as stated in the protocol.		C. Evans
07/01/98	14	091	Annual Report	IDEC to FDA	S. Fino for A. Wei sent the Annual Report for the reporting period of March 1997 through February 1998. All portions of 106-03 clinical study are being conducted by a C.R.O. Pharmaceutical Research Associates (PRA). For Protocol 106-04, IBAH will conduct Good Clinical Practices audits and independent contract clinical monitors will conduct site visits under management of IDEC personnel.		S. Fino
06/30/98	14		Voicemail	FDA to IDEC	M. Fauntleroy left voicemail for A. Wei hoping to catch her ñ He said, ìweíll play tag later.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
06/29/98	14		Voicemail	FDA to IDEC	Michael Fauntleroy left voicemail for A. Wei to give a call back and unable to give details at this time ñ Call back hopefully before 2:00 - he had appointments.		
06/26/98		090	Protocol Amend. New Investigator	IDEC to FDA	A. Wei submits clinical documentation for two new investigators and supplemental site documentation for four additional sites for our Phase III protocol 106-04.		S. Fino
06/17/98	14	No #	CD Rom	IDEC to FDA	A. Wei sent as requested by Michael Fauntleroy on 5/9/98 a CD Rom containing the electronically formatted documents for: Protocol 106-04 Amend. #1 Sr.#083, and Amend. #2 Sr.#088, Protocol 106-05 Sr.#084, Protocol 106-06 Sr.#089 and Certification stating the CD is free of viruses.		
06/15/98	14	089	Protocol Amend. New Protocol	IDEC to FDA	A. Wei is submits a new Phase II protocol 106-06 for patients with B-Cell Non-Hodgkinís Lymphoma Who Have Not Responded to Prior Rituximab therapy. This study will consist of approx. 30 patients among approx. 30 participating sites. An electronic copy will be forwarded tomorrow under separate cover.		S. Fino
06/05/98	14	088	Protocol Amend. Change in Protocol	IDEC to FDA	A. Wei submits an original protocol incorporating Amend. #2. This Amend. is for our Phase III protocol, 106-04. Purposes for Amend. #2 are the following: **1.**To include patients whose tumor histology has transformed from low grade or follicular to intermediate grade -- **2.** To add a third stratification subgroup -- **3.**To replace Appendix G with the updated adverse event definitions as listed in the 4/56/98 FDA Code of Regulations, **-4.** To revise the Activities Flow Chart (APPX A) for the IDEC-Y2B8 treatment arm to distinguish the activities required. An electronic copy will be forwarded next week.		
06/02/98	13	087	Protocol Amend. New Investigators	IDEC to FDA	A. Wei submits new investigator information and updated clinical documentation for four additional sites for our Phase III protocol 106-04 and updated information.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
05/28/98	13		Telecon	IDEC to FDA	A. Wei and S. Fino called Dr. George Mills to schedule date for the Imaging Working Group Meeting. Dr. Mills anticipates meeting for Sept. 23. The forum is informal and the information package doesn't require much review time. He clarified the information package should be sent directly to him rather than submitted to the IND.		
05/21/98	13	086	Protocol Amend. New Investigators	IDEC to FDA	C. Evans for Alice Wei submits a protocol Amend. consisting of the addition of two new investigators for Phase III protocol 106-04 .		C. Evans
05/14/98	13		Letter	IDEC to Roswell Park Cancer Center	A. Wei sent letter to the attention of James Karr, PhD. authorizing Myron Czuczman access to IND applications for Y2B8/IDEC-In2B8 (BB-IND 4850) and Rituxan (Rituximab) (BB-IND 4904) We are investigating these products for the treatment of Non-Hodgkin's B-cell lymphoma. Also this letter serves to inform that currently FDA has not placed any "clinical holds" on these applications. (Also same letter in BB-IND 4904 chron.).		
05/13/98	13	085	Protocol Amend. New Investigators & Change in Protocol	IDEC to FDA	A. Wei submits a change in protocol and new investigator information for our Phase III protocol, Protocol 106-05. New investigator clinical documentation for two study sites:		
05/13/98	13		Telecon	FDA to IDEC	M. Fauntleroy called Cher Palahang and asked if IDEC could send via disk the 5/12/98 submission he received on 106-05. He requested it be sent Win 95, Word 7.0 - or Win 95 Word 6.0. If document is in Win 97 Word 7.0 he won't be able to read it. He would like future active protocols utilizing radio pharmaceutics to be sent electronically to avoid dealing with the document control room.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
05/12/98	13	084	Protocol Amend. New Protocol New Investigator	IDEC to FDA	A. Wei submits a new Phase II Protocol. This protocol describes a multi-center, open-label, single-arm clinical study in patients with relapsed or refractory, low grade or follicular NHL patients who have mild thrombocytopenia. We do not regard this study to be of "pivotal" trial design. New investigator for protocol 106-05.		
05/09/98	13		Voicemail	FDA to IDEC	Michael Fauntleroy called to request some CD Roms with the revised version of the protocol on it. The newest version in accordance with our 6/5/98 submission. George scans them into electronic media. Submit as a Windows 95 Word 7 document. If running Windows 97 use Word 6.		
05/09/98	13		Voicemail	FDA to IDEC	Michael Fauntleroy called again regarding the revised protocol Amend... Requests submitting the entire protocol including its revisions in its entirety on a CD Rom but as an addendum to that other section - the actual text of the revisions.		
05/05/98	13		Voicemail	FDA to IDEC	Michael Fauntleroy left voicemail for A. Wei to inform her that he received IDEC Amend. for protocol 106, our pivotal trial with revisions and have routed it to the review team. He apologized and stated not to call before two weeks have elapsed before they get it to get feedback. A 2 to 3 week window would probably be the most productive due to need to get a statistical review buy off on this.		
05/01/98	13	083	Protocol Amend. Change in Protocol	IDEC to FDA	A. Wei submits an original protocol incorporating Amend. #1. This Amend. is for our Phase III protocol. Original submitted on 12/8/97 #067. The purposes of the Amend. #1 are listed numerically 1 through 19.		
04/30/98	13		Voicemail	FDA to IDEC	Michael Fauntleroy left voicemail for A. Wei requesting a return phone call to either himself or George Mills with Christine White so they can tie up the telecon and the node issue for the 3cm palpable node vs. CT saying that they weren't of that size and they were multiple nodules. He would like to draw that issue to a close.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
04/29/98	13		FDA Telecon	IDEC to FDA	A. Wei, C. White, S. Fino of IDEC and M. Fauntleroy, G. Mills of FDA held a teleconference to discuss the following, MIRDOSE software use referenced in PI, Central dosimetry for future trials, Imaging working group meeting schedule, 106-05 (dose reduction trial) and Requirement of 3 cm lesion for trial accrual.		
04/27/98	13		Fax	IDEC to FDA	A. Wei sent a fax to Michael Fauntleroy of an agenda for our teleconference with him and George Mills, scheduled for 04/28/98. The agenda is as follows: 1) MIRDose software reference in PI 2) Central dosimetry for future trials 3) Imaging Working group meeting schedule 4) 106-05 (dose reduction trial. IDEC participants for the telecon will be A. Wei, C. White and S. Fino.		
04/23/98	13	082	Protocol Amend. New Investigator Clinical	IDEC to FDA	A. Wei submits new investigator information for Phase III protocol 106-04. Enclosed is clinical documentation.		
04/13/98	13	081	Protocol Amend. New Invest. Info. Amend. Clinical	IDEC to FDA	A. Wei submits a Protocol Amend. In this submission new investigator clinical documentation for five study sites and supplemental clinical documentation for one study site for a complete copy of the IRB approved informed consent document that supersedes prior submission #080 - a missing page.		
03/24/98					Inserted Master File letter from Parke-Davis into MF-7087 and in Cross-Reference Binder.		
03/19/98	12	080	Protocol Amend. New Investigator	IDEC to FDA	S. Fino for A. Wei submits a Protocol Amend. - New Investigator information for Phase III protocol, 106-04. Enclosed is clinical documentation . Signature page of Informed Consent Form missing but will be forwarded,		S. Fino

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
03/13/98	12	No #	Electronic Submission	IDEC to FDA	A. Wei submits a letter to Michael Fauntleroy, enclosing 2 CD Rom's containing the following documents: Protocol 106-04 all appendices, Investigator's Brochure for IDEC-Y2B8, CRF's, the Model Informed Consent and a Certification stating that the CD's are free from viruses. They are formatted in Word 6.0 the CRF's are in PDF file format. We did not have a copy of the CD's for our files. Only took Xerox copies of the covers to show what went out. (Y2B8 Test 002 & 003.) **NO SERIAL NUMBER ASSIGNED**		
03/11/98	12		Voicemail	FDA to IDEC	M. Fauntleroy left voicemail for A. Wei apologizing for the hours. He said as long as it is a word 6.0 document out of Windows 95 no problems. If it's a word 90, 8.0 or 7.0 document out of Win 97 there are translation errors that render the document useless. Michael said send all the protocol info and an electronic document of the Amended protocol.		
03/07/98	12		Voicemail	FDA to IDEC	M. Fauntleroy left a voicemail for Alice Wei on Saturday know that she wasn't there and asking a favor by sending a copy of IDEC 106-04, pivotal trial and any other protocols currently running with radiolabeled monoclonal antibodies. They are getting ready for an upgrade to a new system or viewing, electronic doc's, protocols, info database, etc. He's preparing for the eventual.		
03/05/98	12	079	Protocol Amend. New Invest. Info Amend./Clinical	IDEC to FDA	Alice Wei submits new investigator information for Phase III protocol 106-04 - originally submitted on 12/8/97 sr#067.		
02/26/98	12	078	Protocol Amend. New Invest. Info. Amend./Clinical	IDEC to FDA	S. Fino for Alice Wei submits a Protocol Amend../Info. Amend.. New Investigator. Enclosed is an updated 1572.		S. Fino

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
02/26/98	12	077	Protocol Amend. New Invest. Info. Amend./Clinical	IDEC to FDA	EJ Brandreth for Alice Wei submits a Protocol Amend../Info Amend.., consisting of clinical documentation.		E.J. Brandreth
02/25/98	12		Letter	FDA/HHS to FDA (Internal)	Letter from Satish C. Misra /HHS - Public Health Service sent letter to George Mills stating the sponsor has incorporated most of their suggestions in the revised protocol including an interim analysis but no mention of Data Safety & Monitoring Board.		
02/20/98	12		Facsimile	FDA to IDEC	M. Fauntleroy faxed a Federal Register notice to Alice Wei on Developing Regulations for In Vivo Radiopharmaceuticals Used For Diagnosis and Monitoring; Public Meeting. On the fax cover sheet he stated it was an open forum on 2/27/98 - and he would see Alice at the meeting.		
02/19/98	12	076	Protocol Amend. New Invest. Info. Amend./Clinical	IDEC to FDA	Alice Wei submits a Protocol Amend../Info. Amend. New Investigator information for Phase III protocol 106-04 - enclosed is clinical documentation for **Dr. Leo Gordon** Northwestern Univ. Chicago, IL.		
02/13/98	12	075	Prot. Amend. New Invest. Info. Amend./Clinical	IDEC to FDA	Alice Wei/Susette Fino submits a new investigator information Amend.. for our Phase III protocol, 106-04. Enclosed is clinical documentation for three study sites.		S. Fino
01/30/98	12	074	Response to FDA Request for Info.	IDEC to FDA	Alice Wei notes receipt of CBER's letter dated 12/20/97 noting Agency comment and request for additional info. regarding the Phase III pivotal study protocol 106-04. IDEC received further clarification on several items raised by the Agency through a 16 December 1997 telecon. Enclosed is our response to 12/20/97 letter and Protocol 106-04 dated 1-22-98.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
01/27/98	11	073	Information Amend. Clinical	IDEC to FDA	Alice Wei enclosed three recent abstracts on IDEC-Y2B8. The first two are submitted for the Society of Nuclear Medicine 1998 Annual Meeting in 6/98. The third is submitted for the 34th Annual Meeting of the American Society of Clinical Oncology in 5/98.		S. Fino
01/22/98	11	072	Information Amendment CMC	IDEC to FDA	Alice Wei submits a request a change in the title of BB-IND 4850 from 'Indium-IN-111 Radiolabeled Murine Monoclonal (2B8-MX-DTPA) and Yttrium-Y-90 Radiolabeled Murine Monoclonal (2B8-MX-DTPA) to CD20. Indium-In-111 Radio labeled Murine Monoclonal (2B8-MX-DTPA) and Yttrium-Y-90 Radiolabeled Murine Monoclonal (2B8-MX-DTPA) to CD20 The granulocyte colony-stimulating factor is no longer being investigated as part of the clinical study and therefore, no longer relevant to the title of this BB-IND. Enclosed in this submission is clinical site lot release information (App. A). Appx. C letter from Mallinckrodt Inc. authorizing reference to NDA 19-841 In-[111]-Chloride Ster. Soln.		
01/16/98	11	071	Response to FDA Request for Information	IDEC to FDA	Alice Wei submits our response to CBERs letter. This submission includes responses for all four points identified in CBERís letter. Presented is CBERís comments followed by IDECís remarks. Our conclusion is that there were no lots of withdrawn materials used in the manufacture of this product.		S. Fino
01/12/98	11		Phone Convo.	CBER to IDEC	Michael Fauntleroy called Alice and Cher picked up the phone. He has asked that Alice start signing the submission in blue pen. He claims that we are not sending originals of the signature page.		
01/09/98	11	070	Safety Report	IDEC to FDA	Alice Wei submits an IND Safety Report: Initial Written Report for patient number 106-03-02-317 (initials SLB), 47 year-old male with B-cell non-Hodgkinís lymphoma. The mfg. report number 4850-012.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
01/09/98	11	069	Information Amend. CMC	IDEC to FDA	Alice Wei submits an Information Amend: CMC containing lot release data for the IN2B8/Y2B8 Radio labeling Kit drug product. The Kit drug product was filled and finished at Parke-Davis, Rochester, MI. C of Aís enclosed.		
12/30/97	11		Letter	FDA/HHS to IDEC	S. Risso Director/CBER Reviewed our IND Application and the 12/3/97 fax IDEC may proceed but are requesting additional information. **1)** They recommend either increasing study sample size or incorporating an interim analysis. **2)** Requested to submit written confirmation of IDEC analysis plan. **3)** Provide quantitative description of efficacy variables.		
12/16/97	11	068	IND Safety Report		A. Wei sent an initial written IND Safety Report for patient number 106-03-02-327 (initials LPJ). This patient was enrolled in IDEC Protocol 106-03. The mfg. report number is 4850-011.		
12/15/97	11		Voicemail	FDA to IDEC	M. Brunswick called A. Wei and left his number (301)-827-0720 please call him. **Not found in binder.**		
12/11/97	11		Letter	FDA/HHS to IDEC	Kathryn Zoon/Director CBER sent letter stating that several lots of human blood-derived materials including albumin and transferrin have been withdrawn from the market because the lots were manufactured from plasma pools containing units collected from donor(s) subsequently diagnosed with Creutzfeldt-Jakob Disease (CJD) or at increased risk for development of CJD. A list of withdrawn human blood-derived materials is enclosed. She requested to be notified of any additional products that may not be on the list.		
12/08/97	11	067	Protocol Amend. New Prot. New Invest.	IDEC to FDA	A. Wei submits to Jay Siegel/CBER a Protocol Amend.. /New Protocol (106-04) and New Investigator- Clinical documentation included.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
12/08/97	11		Facsimile	IDEC to FDA	A. Wei faxed M. Fauntleroy enclosing the Letter of Understanding highlighting the statistical revisions that were discussed during the Nov. 26th telecon. A. noted her wish to briefly address item 1 regarding the sample size and interim analysis. A. will contact Mr. Fauntleroy to schedule this telecon with him and Dr. Satish Misra. This fax note was also sent to Dr. Mills on 12/3/97.		
12/03/97	11	066	Letter re: Telecon	IDEC to FDA	A. Wei sent a letter stating there was a Nov. 26, 1997 telecon held between G. Mills, Satish Misra and M. Fauntleroy of CBER and IDEC Pharm to discuss statistical considerations for the Phase III pivotal protocol 106-04/ IDEC is pursuing the use of Y2B8 for treatment of patients with low-grade or follicular, B-cell NHL. During that conversation IDEC & FDA agreed to three statistical revisions.		
12/03/97	11	065	Protocol Amend. Change in Protocol	IDEC to FDA	A. Wei submits to Jay Siegel/CBER a Protocol Amendment containing a change in Protocol and a clinical information Amendment containing clinical documentation for four study sites. **106-03-02, 106-03-05, 106-03-07, 106-03-09.**		
12/03/97	11		Facsimile	IDEC to FDA	A. Wei faxed G. Mills enclosing the Letter of Understanding highlighting the statistical revisions that were discussed during the Nov. 26th telecon. A. noted her wish to briefly address item 1 regarding the sample size and interim analysis. A. Wei will contact Mr. Fauntleroy to schedule this telecon with him and Dr. Satish Misra.		
11/19/97	11		Voicemail	FDA to IDEC	M. Fauntleroy left message for A. Wei regarding the pivotal trial protocol. IDEC will be receiving a letter with clinical comments detailing the points of concern for this protocol. M. Fauntleroy stated having the statistician's draft comments to be incorporated with the clinical comments. He said to call G. Mills and work from there.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
11/19/97	11		Voicemail	FDA to IDEC	M. Fauntleroy returned A. Wei's voicemail message. He stated the clinical side is a go. The statistician is still out, should have his review in hand by 10:00 tomorrow and should be able to give A. some guidance regarding the pivotal trial.		
11/09/97	11		Voicemail	FDA to IDEC	M. Fauntleroy/CBER left message for A. Wei to let her know he was trying to get individuals to respond to an e-mail stating that a telecon wasnít necessary. G. Mills affirmed that he was trying to get a few people to call and say that we may proceed with the Phase III trial upon submitting the final.		
11/03/97	SEE NOTE		Letter	IDEC to USANC	A. Wei sent a response to Sandra Van Laan, Technical Associate, United States Adopted Names Council, AMA regarding her letter of 24 Sept. 1997 requesting additional information on IDEC's USAN application for IDEC-Y2B8-MX-DTPA. Data not available identifying the specific amino acids to which the DTPA has been attached. Enclosed was a recent article: *Radiometal Labeling of Immunoproteins: Covalent Linkage of 2-(4-Isothiocyanatobenzl) diethylenetriaminepentaacetic Acid Ligands to Immunoglobulin. Bioconjugate Chemistry, 1990, 1:59.* **(THIS INFO ALSO ENTERED IN USAN AND THAT'S WHERE THE PHYSICAL DOCUMENT IS).**		
10/31/97	11		Voicemail	FDA to IDEC	G. Mills left voicemail for A. Wei requesting a return phone call from either A. or Christine White.		
10/24/97	9	064	Protocol Amend. C.I.P.& Change of Investigator Info Amend. Clinical	IDEC to FDA	A. Wei sent a Protocol Amendment Change in Protocol/ Change of Investigator, Information Amendment Clinical. Protocol 106-03 is entitled A Phase I/II Clinical Trial to Evaluate the Safety and Clinical Activity of IDEC-Y2B8 Administered to Patients with B-Cell Lymphoma. This change in protocol is Amend.. #4. Clinical documentation for five study sites.		

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10/21/97	9		Facsimile	IDEC to FDA	A. Wei sent G. Mills and M. Fauntleroy, CBER, a fax requesting a teleconference to finalize the study design for protocol 106-04. Attached is a copy of the Rituximab 120 day update of efficacy data submitted to BLA 97-0260 (June 16, 1997, serial no. 004). The IDEC-Y2B8 120-day Efficacy Update would be modeled after this document.		
10/17/97	9	063	Draft Protocol 106-04	IDEC to FDA	A. Wei sent a Draft Protocol (106-04) entitled A Randomized, Phase III Multi-Center, Controlled Trial to Evaluate the Efficacy and Safety of IDEC-Y2B8 Radioimmunotherapy Compared to Rituxan Immunotherapy of Relapsed or Refractory Low-Grade or Follicular Non-Hodgkin's Lymphoma. protocol 106-04 incorporates recommendations made by CBER during a September 30, 1997 meeting between CBER personnel and IDEC.		
10/15/97	9		Telecon	IDEC & FDA	IDEC Participants: A. Grillo-Lopez, D. Shen, A. Wei, C. White, S. Fino. FDA Participants: G. Mills, M.D., Medical Reviewer, M. Fauntleroy, CSO. Participants discussed the proposed modifications made to pivotal Protocol 106-04 (submitted to FDA in a 10/13/97 fax). Dr. Mills stated that IDEC should submit the Rituximab 120 Day efficacy update and file the draft protocol with the BB-IND. Dr. Mills is comfortable with the Protocol and anticipates quick movement providing IDEC responds to FDA suggestions.		
10/13/97	9		Facsimile	IDEC to FDA	A. Wei sent M. Fauntleroy, CBER, FDA, a fax requesting a teleconference. IDEC has incorporated a number of FDA suggested changes to the pivotal IDEC-Y2B8 Protocol 106-04 and would like to discuss them before submission. Attached are sections 2.0 OBJECTIVES, 3.0 STUDY DESIGN, and 11.0 STATISTICAL CONSIDERATIONS.		
10/07/97	9		Voicemail	FDA to IDEC	M. Fauntleroy, FDA CBER, left a voicemail for A. Wei regarding a missing back page from a MedWatch form for submission serial # 061. He requested IDEC resubmit with the appropriate information.		

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IDEC-Y2B8 Zevalin (ibritumomab tiuxetan)

DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
10/06/97	9	062	Information Amendment CMC	IDEC to FDA	A. Wei sent Jay Siegel an Information Amendment: CMC containing lot release data for Rituxan drug product lot numbers E9003A, E9026A, and E9028A and bulk drug substance lot numbers E12807-1, E12807-2, E12807-3, E14608-1, and E14608-2. The finished product was produced at Genentech. The bulk drug substance was manufactured at both IDEC and Genentech.		
10/04/97	9		Voicemail	FDA to IDEC	M. Fauntleroy, FDA CBER, left a voicemail for A. Wei requesting meeting minutes from the Sept. 30 FDA Pre-Pivotal Trial Phase III meeting		
10/03/97	9	061	IND Safety Report	IDEC to FDA	A. Wei sent IND Safety Report: Initial Written Report for three patients enrolled in IDEC Protocol 106-03 who received more than the ceiling dose of IDEC-Y2B8. Attached were the completed FDA Form 3500Avs for use in the study. The mfg. report numbers: 4850-008, 4850-009, 4850-010.		
10/02/97	9		Voicemail	CBER to IDEC	Bill Purvis of CBER's Advertising and Promotional Labeling Office left a voicemail message for A. Wei regarding a proposed press release for IDEC-Y2B8. He asked that it not be released because of some concerns and wanted to discuss it the following day.		
09/23/97	9		General Correspondence Mtg. Materials	IDEC to FDA	S. Fino sent another nine copies of the above submission, to the attention of M. Fauntleroy. Serial #060.		
09/22/97	9	060	Other: Agenda & Meeting Draft Protocol ñ General Correspondence	IDEC to FDA	A. Wei sent a protocol Amendment consisting of a revised draft protocol (106-04). The draft pivotal trial protocol was previously submitted to BB-IND 4850 on July 14, 1997 (#58) in a request for a pre-pivotal meeting and expedited review. Included is an agenda and a list of attendees for the meeting scheduled to be held with CBER on September 30, 1997.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
09/16/97	9		Memo	IDEC Internal only	J. Leonard sent out a memo re: Imaging Working Group Meeting with FDA Regarding IDEC-Y2B8 Dosimetry Data collection and Analysis.		
09/15/97	9		Facsimile	IDEC to FDA	A. Wei sent Dr. Mills a fax of draft slides outlining the inclusion/exclusion criteria as well as response criteria for protocol 106-04. A. also stated that we could not send the final set of slides as we are still in the process of developing them. (FDA meeting September 30, 1997) Attached were two abstracts on a Phase I/II (106-03) trial with IDEC-Y2B8 radioimmunotherapy. These abstracts have been submitted for the Annual Meeting of the American Society of hematology		
09/12/97	9		Facsimile	IDEC to FDA	A. Wei sent fax with draft slides outlining the inclusion/exclusion criteria as well as the response for protocol 106-04. A. stated that we are still in the process of developing our final slide presentation for the upcoming FDA meeting of 9/30/97, so unable to forward the full presentation.		
07/30/97		059	Protocol Amendment C.I.P. New Investigator	IDEC to FDA	J. Leonard submits an original protocol #106-03 incorporating Amendments #1,2, & 3 a change in protocol information.		
07/23/97	9		Voicemail	CBER to IDEC	G. Mills of CBER left a voicemail message for C. Palahang, regarding setting up a time to put together the details for the imaging working group meeting.		
07/21/97	9		Telecon	IDEC to FDA	J. Leonard spoke to S. Sickafuse, CBER re: the date of the pre-pivotal meeting for this product. IDEC would like the meeting on September 23, 1997 and that an alternative would be September 30, 1997. She indicated she would try to schedule us for the meeting on 09/23/97 from 3 - 4.30pm. She will confirm exact meeting time and date once she determined the availability of the meeting attendees from FDA. Sharon asked for 8 additional sets of the pre-pivotal meeting document. John told Sharon that the additional sets would arrive at FDA later this week.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
07/16/97	10A & 10B	058	Request for Pre-Pivotal Meeting	IDEC to FDA	IDEC submits four volumes: Request for Pre-Pivotal Meeting and Expedited Review.		
07/01/97	9		Telecon	IDEC to FDA	C. White, D. Shen, A. Solinger and J. Leonard called Dr. Mills to discuss the agenda for the Imaging Working Group meeting and to provide him with an update of the status of the pre-pivotal meeting document. Dr. Mills indicated that the agenda was fine. J. Leonard then spoke with M. Fauntleroy and asked that IDEC be scheduled for a pre-pivotal meeting in advance of making the submission on July 16. He could not grant this request, but we would most likely be scheduled for our pre-pivotal meeting during the week of September 22.(23/25).		
06/05/97	9	057	Protocol. Amend Change Invest. Clinical Info. Amend.	IDEC to FDA	Protocol and Information Amendment: IRB annual renewal in addition to clinical documentation for a change of Investigator for **Dr. Ivor Royston,** Sidney Kimmel Cancer Center, San Diego, CA for Protocol 106-03.		
05/28/97	9	056	Response to CMC Amend.	IDEC to FDA	Response to CMC Amendment comments and x-reference to BB-MF 7087.		
05/21/97	9	055	Minutes of Two FDA Telecons	IDEC to FDA	J. Leonard and A. Grillo-Lopez had a teleconference with Dr. G. Mills, CBER medical reviewer for IDEC-Y2B8 on 2/6/97 to discuss the implementation of response criteria for IDEC-Y2B8 pivotal trial. Second teleconference on 3/13/97 John Leonard, John Geigert and Chris Burman called M. Brunswick, product reviewer to address the use of 2B8 antibody and how to assess comparability.		
05/12/97	9	054	Information Amendment CMC	IDEC to FDA	Information Amendment Cross-reference Genentech, Inc. Type II Master File BB-MF 6601.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
04/30/97	9	053	Annual Report	IDEC to FDA	Annual Report for Indium-In-111 Radiolabeled and Yttrium-Y90 Radiolabeled Murine Monoclonal Antibody (2B8-MX-DTPA) to CD20; Bone Marrow and Granulocyte Colony-Stimulating Factor for the reporting period of March 1996 through February 1997.		
03/27/97	9	052	Protocol Amend. New Investigator	IDEC to FDA	Protocol Amendment for Phase I/II Protocol 106-03. Two Amendments have also been submitted: Protocol Amend. #1 on 06/06/96 and #2 on 08/14/96.		
03/24/97	9		Letter	FDA to IDEC	Acknowledgment by FDA (M. Fauntleroy, CSO) of receipt of IDEC Type II MF for Murine Monoclonal Antibody (2B8) to CD20 and assignment of No. BB-MF 7087.		
03/13/97	9		Telecon	IDEC to FDA	J. Leonard and C. Burman (IDEC) called M. Brunswick (FDA, CBER) to address 1) Use of CHO-Produced (Torreyana) 2B8 Antibody in Phase II and Pivotal Trials, and 2) Demonstration of Comparability between IDEC- and Covance-Produced IDEC-2B8 Antibody and 2B8-MX-DTPA Conjugate.		
02/26/97	NOW IN BB-MF 7087	051	Information Amend.	IDEC to FDA	Information Amendment describing manufacturing of the IDEC 2B8 CHO produced antibody and the filling operation performed by Park-Davis. **05/21/97 - This submission is now to be found under BB-MF 7087, Volume 1.**		
02/20/97	8	050	Info Amendment Interim Report	IDEC to FDA	Interim report for Protocol 106-03 (also to be submitted in C2B8 BLA) (Footer of document says BLA/ C2B8)		
02/18/97	8		Telecon	FDA TO IDEC	Between J. Leonard and M. Brunswick: Licensure process will be reviewed by FDA Ombudsman, but not expected to change. Ref. intercenter agreements (11/91)		
02/06/97	8		Telecon	IDEC to FDA	IDEC telephoned G. Mills, CBER, to review information sent to him late last week and to discuss the implementation of response criteria for the Y2B8 pivotal trial.		
02/05/97	8		Telecon	IDEC to FDA	Call to confirm the licensure process of application to CBER by IDEC and separate NDA by yttrium manufacturer. M. Brunswick agrees with process.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
01/30/97	8		Telecon	FDA to IDEC	G. Mills and Dr. Litwin called JEL regarding the status of Y2B8 phase I/II project and the development of the dosimetry protocol for the pivotal trial, draft protocol, and Phase II results should be submitted at least six weeks before pre-pivotal meeting and plan to meet with Imaging Working Group, FDA prior to pre-pivotal meeting. Fax copy of Weisman abstract to him.		
01/28/97	8		Facsimile	IDEC to FDA	J. Leonard sent letter to G. Mills with attention that Dr. Jerian described the SWOG response criteria at the BRM meeting, her slides are included.		
01/27/97	8		Telecon	FDA to IDEC	Dr. Mills to JEL re: Checking on status of Phase I trial and pre-pivotal meeting. JEL informed him that pre-pivotal meeting now planned for June; add dosimetry guidelines to Investigator Brochure for a unified approach; fax copy of SWOG criteria to him; any concerns re: radio labeling process at sites? He had no concerns but should check with Mark Brunswick.		
12/13/96	8	049	IND Safety Report	IDEC to FDA	John E. Leonard submits an IND Safety Report: Initial Written Report for death of patient No.#106-03-03-203. The mfr. report number AE 4850-007.		
12/11/96	8	047	Gen. Corresp. Address Change	IDEC to FDA	Change of address for John Leonard from Torreyana to Callan.		
12/05/96	8		Telecon	IDEC to FDA	John Leonard, Regulatory Affairs, IDEC called Mr. Michael Fauntleroy, CBER, FDA regarding the death of Patient No. 203 in Protocol 106-03.		
12/03/96	8	048 (date out of order)	New Investigator	IDEC to FDA	New investigator information is submitted for Protocol 106-03.		
11/12/96	8		Telecon	IDEC to FDA	Telecon between John Leonard, IDEC, and M. Brunswick, product reviewer regarding the possibility of eliminating the use of the immunoreactivity assay (binding kits) by the clinical sites.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
11/11/96	8	046	Response to FDA Request for Information	IDEC to FDA	General Correspondence: Response to FDA request for Information. Enclosed List of Investigators and Case Report Form copies for Protocol 106-03 for study 'A Phase I/II Clinical Trial to Evaluate the Safety and Clinical of IDEC-Y2B8 Administered to Patients with B-Cell Lymphoma.		
10/28/96	8		Telecon	FDA to IDEC	George Mills, M.D., Medical Reviewer called to provide his impressions of the Phase I/II protocol.		
10/25/96	8	045	Protocol Amend. New Investigator	IDEC to FDA	IDEC submits a Protocol Amend: New investigator - **Leo Gordon**, Northwestern Univ.		
10/25/96	8		Telecon	FDA to IDEC	George Mills, M.D., Medical Reviewer for this IND called to discuss the Phase I/II protocols filed last August, re our approach, progress and clinical development plans.		
10/08/96	7	044	Information Amend. Clinical Study Report	IDEC to FDA	Information Amend..: Clinical- Clinical Study Report for IDEC Protocol 1315, No. 106-01-02. (CONSISTS OF 3 VOLUMES)		
10/07/96	6	043	Protocol Amend. New Investigators	IDEC to FDA	IDEC submits a Protocol Amend New Investigators.		
09/16/96	6	042	IND Safety Report	IDEC to FDA	John E. Leonard submits an IND Safety Report: Initial Written Report for patient No.#10603-02104 (Initials FGS). IDEC received this safety report on 09/03/96. The mfg. report number AE 4850-006.		
08/23/96	6	041	Annual Report	IDEC to FDA	IDEC submits Annual Report for period March 1995 through February 1996 submitted to Jay Siegel, Acting Director, FDA.		
08/14/96	5b	040	Protocol Amend. Change in Protocol New Investigator	IDEC to FDA	IDEC submits Protocol Amend. Change in Protocol/New Investigator Amends #1 & #2 for Protocol 106-03. Also IDEC submits Protocol Amend.. documentation for		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
08/01/96	5b		Telecon	IDEC to FDA	Participants: IDEC/John E. Leonard, Ph.D. and Mr. M. Fauntleroy from CBER. Subject: Use of indium-[111] chloride material produced by Mt. Sinai/Cyclotron Consulting Group, Coral Gables, FL and cross-reference letter authorizing FDA review of Mt. Sinai's Master File.		
07/18/96	5b	039	Protocol Amend. New Invest.	IDEC to FDA	IDEC submits a Protocol Amend..: New Investigator - information.		
06/07/96	5b	038	Information Amendment CMC Lot Release	IDEC to FDA	IDEC submits an Information Amend.: Chemistry, Manufacturing & Control (Lot Release) containing product release data for the In2B8/Y2B8 Radio labeling Kit (lot 0147) and the kit components, formulation buffer (lot 0143), Low-Metal Sodium Acetate (lot 0144), 2B8-MX-DPTA (lot 0139) and Reaction Vial, (lot 0146).		
06/06/96	5b	037	Pro. Amend.: New Invest. Change in Pro.	IDEC to FDA	IDEC submits a Protocol Amend..: Change in Protocol/New Investigator Amend. #1. Also included is clinical information for two co-principle investigators.		
05/17/96	5a	036	Info Amend. Chemistry Microbiology Pharm/Tox	IDEC to FDA	IDEC submits an Information Amend: Chemistry/Microbiology - Pharmacology/Toxicology -Several documents relating to the manufacture and pre-clinical test the components of a radio labeling kit, and the use of this kit for the [90]-yttrium and [111]-indium labeling of the murine ant-CD20 antibody conjugate termed 2B8-MX-DTPA. (TWO VOLUMES CONSISTS OF 350 PAGES)		
04/22/96	4		Telecon	IDEC to FDA	J. Leonard called M. Brunswick regarding the use of Westinghouse-Hanford 90Yttrium. M. Brunswick expressed concern over Westinghouseís lack of sterility testing and that he would need to discuss it with his counterparts at CDER.		
03/14/96	4	035	Information Amend.ment Clinical Study Report	IDEC to FDA	IDEC submits a Information Amend.: Clinical - Clinical Study Report for IDEC Protocol 1320, Report No. 106-01-01, entitled "A Phase I/II Clinical Trial Yttrium-[90]-Labeled IDEC-2B8 Given Every Six to Eight Weeks to Patients with B-Cell Lymphoma."		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
12/22/95	4	034	Prot Amend./New Prot./Letter Cross Ref. IND 4904	IDEC to FDA	IDEC submits a Protocol Amend. New Protocol : Letter of Cross-Reference to BB-IND 4904 (IDEC Protocol 106-03).		
10/10/95	4	033	FDA Request for Information	IDEC to FDA	IDEC submits FDA Request for Information regarding description of clinical response classifications we are requesting to use in our registration trial.		
10/06/95	4		Telecon	IDEC to FDA	J. Leonard called G. Mills (CBER) to ask if Phase I/II protocol using IDEC-C2B8 with IDEC-Y2B8 could be submitted to the existing Y2B8 IND. G. Mills stated that the Phase I/II protocol and letter of cross-reference of Y2B8 IND would be acceptable, without the need for filing a new IND.		
09/26/95	4	032	FDA Request for Information Withdrawal of Mtg	IDEC to FDA	IDEC submits a Request for Information: Withdrawal of Meeting Request a meeting between IDEC and CBER. Additionally included are minutes of teleconferences between IDEC and CBER from 08/31/95 - 09/08/95.		
09/08/95	4		Telecon	IDEC to FDA	A. Grillo-Lopez, D. Shen, B. Dallaire, A. Solinger and J. Leonard called G. Mills and M. Brunswick (CBER) to discuss various issues raised by G. Mills in teleconference on 8/31/95.- TWO sets of minutes 1 paginated 1 not.		
08/31/95	3b		Telecon	IDEC to FDA	J. Leonard telephoned G. Mills, CBER, to confirm time for requested teleconference. Dr. Mills asked that IDEC respond to a number of issues in the upcoming teleconference.		
08/28/95	3b		Telecon	FDA to IDEC	B. Shaw called J. Leonard at the request of Dr. Mills requesting a teleconference with IDEC on either Sept. 6, 7 or 8, 1995, to discuss dosimetry data collection during upcoming clinical trial. J. Leonard later called B. Shaw with tentative meeting times on Sept. 7-8, 1995.		
08/23/95	3b	031	Request for Meeting	IDEC to FDA	IDEC submits a Request For a Meeting between IDEC and CBER personnel to discuss the initiation of a Phase II/III clinical trial to further characterize the treatment using the product referenced. Consider dates: 9/19, 21, 26, or 28, 1995.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
08/16/95	3a		Telecon	IDEC to FDA	IDEC telephoned M. Brunswick to discuss development of a CHO Protein Assay for C2B8.		
08/16/95	3a	030	Meeting Deferral	IDEC to FDA	IDEC submits a Meeting Deferral - a formal request to cancel 09/14/95 meeting.		
08/11/95	3a		Telecon	IDEC to FDA	It was decided between J. Leonard and K. Schneider of FDA to postpone a 09/14/95 meeting that was set up to discuss clinical and manufacturing information relating to IDEC-Y2B8. IDEC may need to return to FDA for a manufacturing meeting once data has been collected from the manufacturing process. K. Schneider also asked IDEC to submit a letter to the IND formally requesting cancellation of the 09/14/95 meeting.		
08/07/95	3a		Telecon	IDEC to FDA	J. Leonard spoke with Dr. G. Mills of the Office of Therapeutics Research and Review regarding a meeting to discuss the future clinical and manufacturing development of this product. Dr. Mills assured him that there was no doubt that IDEC would need to meet with the FDA. J. Leonard informed Dr. Mills that IDEC would submit to the IND a pre-meeting package and that he should expect these materials to arrive at FDA on or about 08/16/95.		
08/02/95	3a		Telecon	IDEC to FDA	J. Leonard spoke with B. Shaw at CBER regarding a proposed meeting with FDA to discuss future clinical and manufacturing development issues with Dr. Mills and other CBER personnel. Ms. Shaw stated that she was not sure the meeting would even be warranted and a teleconference would suffice. She also stated that there may be some scheduling conflicts and suggested that we propose additional meeting dates in the last two weeks of September.		
07/27/95	3a	029	Request for Meeting	IDEC to FDA	IDEC submits a Request For Meeting with CBER personnel to discuss summary information on completed phase I clinical study, outline phase II/III protocol and elements of clinical development plan and discuss proposed manufacturing changes.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
05/11/95	3a	028	Request for Information	IDEC to FDA	IDEC submits a Request for Information - enclosed is a memorandum dated 05/11/95 documenting a teleconference between Dr. G. Mills and M. Fauntleroy of FDA and Dr. Grillo-Lopez, B. Dallaire and J. Leonard of IDEC. This memorandum describes a mutually agreed upon mechanism for reporting adverse event information for patients enrolled in future clinical studies conducted with this investigational agent who are hospitalized with grade four hematologic toxicity.		
05/11/95	3a	027	IND Safety Report	IDEC to FDA	John E. Leonard submits IND Safety Report: Follow-up to a Telephonic Report for patient No.#103 (initial JHH) who was hospitalized on December 19, 1994, for fever with grade 3 neutropenia and right auxiliary swelling 27 days post treatment with approximately 40 mCi of 90Yttrium-labeled 2B8-MX-DTPA. The mfr report number AA 4850-005.		
05/08/95	3a		Telecon	IDEC to FDA	J. Leonard spoke to M. Fauntleroy at FDA regarding a 3 day Adverse Event Report for patient no. 103 (initial JHH) enrolled in IDEC Protocol 1315.		
05/05/95	3a	026	Annual Report	IDEC to FDA	IDEC submits an Annual Report for the period of April 1994 through February 1995. Information Amend.: CMC.		
04/27/95	3a		Telecon	FDA to IDEC	J. Leonard received a call from M. Fauntleroy, FDA, regarding the AEís filed to this IND on 04/25/95, asking why these events were reported to FDA so long after they occurred.		
04/25/95	3a	025	IND Safety Report	IDEC to FDA	John E. Leonard submits an IND Safety Report: Initial Written Report for patient No.#117 (initials J-B) who was hospitalized on January 27, 1995, for neutropenic fever 38 days post treatment with 52.8 mCi of 90Yttrium-labeled 2B8-MX-DTPA.The mfr.report number AE 4850-004.		
04/25/95	3a	024	IND Safety Report	IDEC to FDA	John E. Leonard submits an IND Safety Report : Initial Written Report for patient No.#116 (initials G-D) who was hospitalized on January 23, 1995 for leukopenic fever 40 days post treatment with 53.3 mCi of 90Yttrium-labeled 2B8-MX-DTPA. The mfr. report number AA 4850-003.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
04/25/95	3a	023	IND Safety Report	IDEC to FDA	John E. Leonard submits an IND Safety Report: Initial Written Report for patient No.#114 (initials BLV) who was hospitalized on December 23, 1994 for febrile neutropenia 17 days post treatment with 51.7 mCi of 90Yttrium-labeled 2B8-MX-DTPA. The mfr. report number AA 4850-002.		
08/12/94	2b	022	Information Amendment CMC	IDEC to FDA	IDEC submits an Information Amend.: CMC - containing revised product documents for the preparation of indium-[111]- and yttrium-[90]-labeled 2B8-MX-DTPA.		
08/12/94	2b	021	Information Amendment: Clinical ñ Add Sub-investigators	IDEC to FDA	IDEC submits an Information Amend..: Clinical: Addition of Sub-Investigators. - Contains a letter from Dr. S. Knox, adding three sub-investigators who will be assisting Dr. Knox in the conduct of the clinical study.		
07/15/94	2b		Re-titling Letter	FDA to IDEC	FDA acknowledges and approves request to re-title BB-IND 4850 to *Indium-In-111 Radiolabeled and Yttrium-Y-90 Radiolabeled Murine Monoclonal (2B8-MX-DTPA) to CD20: Bone Marrow and Granulocyte Colony-Stimulating Factor.*		
07/08/94	2b	020	Protocol Amendment: C.I.P.	IDEC to FDA	IDEC submits a Protocol Amend. Change in Protocol containing Amend.. #3, dated 05/04/94 to IDEC Protocol 1315. Also contains IRB approval and informed consent documents.		
07/06/94	2b		Telecon	IDEC to FDA	J. Leonard spoke with M. Fauntleroy of FDA and was informed that FDA had re-titled IND 4850 *Indium-In-111 Radiolabeled and Yttrium-Y-90 Radiolabeled Murine Monoclonal (2B8-MX-DTPA) in CD20: Bone Marrow and Granulocyte Colony-Stimulating Factor.* M. Fauntleroy indicated that we should receive a letter from FDA officially communicating this title for the BB-IND 4850. Letter from Nordion International, Inc. & C of As.		
06/23/94	2b	019	Information Amendment Chemistry Microbiology	IDEC to FDA	IDEC submits Information Amend: Chemistry/Microbiology indicating intention to begin using yttrium-[90] chloride solution (from Nordion) for use in IDEC protocol 1315. Chemistry, Manufacturing and Control.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
06/22/94	2b	018	Other: Request Change in BB-IND Title	IDEC to FDA	IDEC submits Request Change in BB-IND 4850 Title - notifies FDA that since requested withdrawal of BB-IND 4851 is now considered complete, per letter signed by Dr. R. Eastep of FDA. IDEC now requests that title of BB-IND 4850 be changed to 'Indium-In-111 and Yttrium-Y-90 Conjugated (MX-DTPA) Murine Monoclonal Antibody (2B8) to CD20.Ó		
05/31/94	2b		Telecon	Telecon IDEC to FDA	CBER representatives F. Kaltovich and M. Brunswick and IDEC representatives, P. Chinn, J. Leonard and A. Wei, discussed the mix and shoot submission for yttrium labeled 2B8. Drs. Kaltovich and Brunswick agreed to allow the use of the mix and shoot protocol to treat six patients and then to evaluate the data from a clinical and product perspective.		
05/25/94	2b		Telecon	IDEC to FDA	P. Chinn and A. Wei telephoned M. Brunswick of FDA to discuss the mix and shoot submission for yttrium labeled 2B8.		
05/24/94	2b		Telecon	FDA to IDEC	M. Brunswick called to discuss the mix and shoot submission for yttrium labeled 2B8. He recommended we contact Florence Kaltovich to further discuss this issue.		
05/18/94	2b	017	Information Amendment CMC	IDEC to FDA	IDEC submits an Information Amend: CMC Amend.: Lot Release Data: 2B8-MX-DTPA Lot M3MXD003 involving new release specifications for the yttrium and indium labeled 2B8-MX-DPTA products.		
05/13/94	2b	016	Information Amendment: CMC	IDEC to FDA	IDEC submits an Information Amendment: CMC - containing documents describing changes in the manufacture of the Yttrium-[90]-labeled 2B8-MX-DPTA presently used in IDEC Protocol 1320.		
05/12/94	2b	015	Info. Amend. Discontinue Clinical Investigation.	IDEC to FDA	IDEC submits an Information Amend: Clinical Discontinuance of Investigation - informs FDA - conducted under IDEC Protocol 1320.		
05/02/94	2b	014	Other: Closure Ltr	IDEC to FDA	IDEC submits a request to close BB-IND 4851.		

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DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
04/29/94	2b	013	Request for Info./ Info. Amend. CMC	IDEC to FDA	IDEC submits annual report for the period of November 1992 - March 1994. In addition, IDEC submits an interim study report for protocol 1315, the unified dosimetry protocol and lot release data.		
04/12/94	2b		Telecon	IDEC to FDA	J. Leonard updated G. Mills regarding preparation of the interim clinical study report.		
04/04/94	2b	012	Protocol Amend. C.I.P.	IDEC to FDA	IDEC submits a Protocol Amend. Change in Protocol. Also submitted is IRB approval letter and informed consent document.		
03/09/94	2b		Telecon	IDEC to FDA	J. Leonard called G. Mills at FDA to ask if patients at Stanford could continue to be treated while we are preparing the interim clinical summary. He agreed as along as we submit our report by 05/01/94. Dr. Mills also suggested that we close BB-IND 4851 as having two IND files for the same program has been causing some confusion at FDA.		
02/18/94	2b		Telecon	IDEC to FDA	Dr. Leonard called Dr. Mills of FDA to inform him of meeting with Dr. Goris of Stanford on 2/16/94. Dr. Mills encouraged J. Leonard to arrange meeting date as soon as possible.		
02/08/94	2b		Telecon	FDA to IDEC	Dr. G. Mills at FDA called asking about dosimetry data from trial being conducted at Stanford. J. Leonard stated that he would be talking to Dr. Goris of Stanford on 2/16/94 and would submit information to FDA soon after. Dr. Leonard discussed several issues with Dr. Mills including upcoming pre-IND meeting with FDA and NCI.		
01/11/94	2b	011	Protocol Amend. C.I.P. Info. Amend/ CMC	IDEC to FDA	IDEC submits a protocol Amend. redefining the entry criteria into IDEC Protocol 1315 and an information Amend.. containing lot release data for lot no. M2B84075 of the 2B8-49 murine monoclonal antibody to CD20 antigen.		
01/03/94	2b		Telecon	FDA to IDEC	Dr. G. Mills called inquiring if we had treated the sixth patient at Stanford University (IDEC Protocol 1315) and added that before treating patient seven, he would like to receive the interim report he requested via telephone on 12/15/93.		

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IDEC-Y2B8 Zevalin (ibritumomab tiuxetan)

DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
12/15/93	2b		Telecon	FDA to IDEC	J. Leonard spoke with Dr. G. Mills regarding status of clinical trials under IDEC Protocol 13 15 and 1320 and asking for an interim report of the activity at Stanford.		
11/15/93	2b	010	Information Amend. CMC	IDEC to FDA	IDEC submits Information Amend.: CMC containing lot release data for two lots of murine anti-CD20 lots antibody 2B8 (Lots M22B8015 and M3B84001) and one lot of 2B8-MX-DTPA lot no. M22B8002.		
11/10/93	2b	009	Information Amend. CMC	IDEC to FDA	IDEC submits Information Amend: CMC containing lot release data for one lot of 2B8-MX-DTPA. Product release documents are for 2B8-MX-DTPA lot no. M3MXD002.		
10/21/93	2b	008	IND Safety Report	IDEC to FDA	Alice Wei submits IND Safety Report - Initial 10 day Report for patient No. 001 (initials REB) enrolled in protocol 1320. The IND Safety Report, received by IDEC on 10/15/93 was from the VA Hospital, San Diego, CA. Manufacturer's report number is AE 4850-001.		
09/27/93	2b		Telecon	FDA to IDEC	Dr. M. Brunswick called stating that the action plan that was submitted to IND was acceptable.		
09/24/93	2b	007	Protocol Amend.. & Information Amendment	IDEC to FDA	IDEC submits protocol Amend. containing IRB approval for UCSD, information Amend.. containing lot release data for lot #M12B8030 and information Amend.. containing pharmacology/toxicology study report which was inadvertently omitted from the original IND.		
09/17/93	2b		Telecon	FDA to IDEC	Dr. G. Mills called asking a variety of questions regarding the high-dose and multiple low-dose yttrium protocols.		
09/13/93	2b	006	Request For Information	IDEC to FDA	IDEC submits response to FDA's request that IDEC, together with bone marrow transplant staff at Stanford University Hospital, develop an action plan describing our efforts to further process the in vitro reagents presently used to lyse lymphoma tumor cells present in the bone marrow of patients treated under Protocol 1315.		

Chronology for BB-IND 4850
IDEC-Y2B8 Zevalin (ibritumomab tiuxetan)

DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
08/23/93	2b		Telecon	IDEC to FDA	J. Leonard spoke with Dr. M. Brunswick asking for a two-week extension of deadline to submit action plan to resolve issue of use of in vitro reagents in bone marrow transplantation. Extension was granted.		
08/20/93	2b		Telecon	FDA to IDEC	R. Dachman and G. Mills, FDA called and spoke with J. Leonard regarding clarifications of some issues about Protocols 1315 (Stanford) and 1320 (UCSD, VA Medical Center and SDRCC).		
07/23/93	2b		Telecon	FDA to IDEC	Dr. M. Brunswick called stating that although IND is not being placed on clinical hold, there are concerns that IDEC must address and submit to the stated time frame.		
07/22/93	2a	005	Protocol Amend. New Investigator New Protocol	IDEC to FDA	IDEC submits a Protocol Amend. New Protocol for protocol # 1320 and new investigator data for Dr. Sam Halpern, VA Hospital, San Diego.		
06/16/93	2a	004	General Correspondence	IDEC to FDA	IDEC notifies FDA of change of address, telephone number and contact person for IDEC Pharmaceuticals.		
06/07/93	2a	003	Protocol Amend.	IDEC to FDA	IDEC submits a Protocol Amend.: Change in Protocol for IDEC 1315. A starting dose 20mCi may be used providing the patients were Robust.		
05/19/93	2a		Telecon	IDEC to FDA	FDA requests information on cellufine sulfate; John Leonard offers to fax requested information to FDA. FDA will be sending a letter containing number of issues requiring resolution prior to entry into phase II clinical trials.		
02/19/93	2a		Telecon	IDEC to FDA	Bridget Binko called Dr. Dachman to discuss review of the supplementary data and the conversations with Dr. Knox. Regarding the starting dose of yttrium-labeled antibody. FDA allows clinical study to commence at the 20mCi Yttrium-labeled dose provided the patients are fairly robust. FDA indicates that prior to commencing phase 2 studies, additional viral validation studies will need to be done and questions regarding stability answered.		

Chronology for BB-IND 4850
IDEC-Y2B8 Zevalin (ibritumomab tiuxetan)

DATE	VOL.	SER #	TYPE	SOURCE	DESCRIPTION	AIRBILL #	ORIGINATOR
01/29/93	2a	002	Request For Information	IDEC to FDA	IDEC submits full reports of thin-section electron microscopy, negative stain electron microscopy, and co-cultivation studies in response to FDA's request for information.		
01/21/93	2a	001	Response to Clinical Hold	IDEC to FDA	IDEC submits response to questions raised by CBER during conference call on 01/07/93. Data outlining the validation and production process that provide viral removal or inactivation were submitted.		
01/07/93	2a		Telecon	FDA to IDEC	Conference call was held to discuss results of CBER's review of initial IND submission. FDA comments and clinical hold issues were discussed. FDA has concerns about purification process and with the initial therapeutic dose of yttrium-labeled antibody being set at 20mCi.		
12/30/92	2a		Telecon	FDA to IDEC	Dr. Dachman, FDA, requests that IDEC should not begin clinical trials until after a conference call is held between IDEC and FDA on 01/06/93, indicating that the viral validation data is deficient.		
12/07/92	2a		Letter	FDA to IDEC	FDA acknowledges receipt of IND and issues IND #4850.		
11/24/92	1a and 1b	000	Initial IND Application	IDEC to FDA	Initial Investigational New Drug Application sent to Dr. Zoon for Yttrium-(90)-Labeled Murine Monoclonal Anti-CD20 Antibody (2B8) (856 pages inc.)Letter from Bridget Binko.		

Exhibit E

Excel Spreadsheet Containing Calculation of Period of Extension

Exhibit E Caculation	**Date - Days**
Patent Information for U.S. Patent 5,776,456:	
Patent Issue Date	July 7, 1998
Non Provisional U.S. Patent Priority Date	June 7, 1995
FDA Information:	
Date IND Becomes Effective	December 7, 1992
Date BLA Submitted to the FDA	November 1, 2000
Date BLA Approved by the FDA	February 19, 2002
IND Period:	
Start Date of Regulatory Review Period	December 7, 1992
BLA Review Period (days)	2886 days
1/2 BLA Review Period (days)	1443 days
Reg. Review Period Allowed:	
NDA/BLA Review Period (days)	475 days
Regulatory Review Period	3359 days
Reg. Review Period 1/2 IND Period (days)	1916 days
Statutory Limitations:	
Patent Expiration Date (17 from issue or 20 year from patent)	July 7, 2015
Expiraiton Under 5 Years Limitation Period	July 7, 2020
Expiration of 14 Years from BLA Approval	February 19, 2016
Expiration Based on Regulatory Review Period	June 20, 2019
Maximum Extension Based on All Limitations:	February 19, 2016
Maximum Aggregate Extension In Days	227 days

Exhibit D

Description of Significant Activities Undertaken During the Regulatory Review Period for Zevalin® and Applicable Dates for Such Activities

Exhibit F

FDA Letter to IDEC Pharmaceuticals Corporation

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our STN: BL 125019/0

FEB 19 2002

Ms. Alice Wei
IDEC Pharmaceuticals Corporation
3030 Callan Road
San Diego, CA 92121

Dear Ms. Wei:

Your biologics license application for Ibritumomab Tiuxetan is approved effective this date. IDEC Pharmaceuticals Corporation, San Diego, California, is hereby authorized to introduce or deliver for introduction into interstate commerce, Ibritumomab Tiuxetan and associated components for the preparation of Indium-111 Ibritumomab Tiuxetan and Yttrium-90 Ibritumomab Tiuxetan under Department of Health and Human Services U.S. License No. 1235.

Ibritumomab Tiuxetan, as part of a specific therapeutic regimen, is indicated for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma, including patients with Rituximab (Rituxan™) refractory follicular non-Hodgkin's lymphoma. The therapeutic regimen includes Rituximab, Indium-111 Ibritumomab Tiuxetan, and Yttrium-90 Ibritumomab Tiuxetan.

Under this authorization, you are approved to manufacture Ibritumomab Tiuxetan, Yttrium-90, and the kits for the preparation of Indium-111 Ibritumomab Tiuxetan and Yttrium-90 Ibritumomab Tiuxetan. Ibritumomab bulk will be manufactured at your facility in San Diego, California. Ibritumomab Tiuxetan and the non-biological kit components will be manufactured, filled, labeled, and packaged into kits at DSM Catalytica Pharmaceuticals, Incorporated in Greenville, North Carolina. In accordance with approved labeling, your product will bear the proprietary name Zevalin and will be marketed as two single-dose kits for radiolabeling with Indium-111 and Yttrium-90, each containing a 3.2 mg vial of Ibritumomab Tiuxetan, a 2 mL vial of 50 mM sodium acetate buffer, a 10 mL vial of formulation buffer and a sterile, empty reaction vial. The Yttrium-90 Chloride Sterile Solution will be manufactured and distributed under contract by *MDS Nordion, Ottawa, Ontario, Canada.*

The dating period for Ibritumomab Tiuxetan drug product shall be 24 months from the date of manufacture when stored at 2 to 8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated bulk. The expiration date for the kit shall be 24 months or less, dependent on the shortest expiration date of any of the components, when stored at 2 to 8°C. The dating periods of the non-biological kit components when stored at 2 to 8°C, shall be 24 months for sodium acetate buffer, 30 months for formulation buffer, and 30 months for the reaction vials. The dating period of the Yttrium-90 Chloride Sterile Solution shall be 5 days when stored at 15 to 30°C. The Ibritumomab bulk may be stored for up to 24 months at 2-8°C.

Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots of each product. The stability protocols in your license application are considered approved for the purpose of extending the expiration dating period of your Ibritumomab Tiuxetan drug product, Ibritumomab bulk, and the non-biological kit components as specified in 21 CFR 601.12.

You are not currently required to submit samples of future lots of Ibritumomab Tiuxetan or the kit to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release specifications.

Any changes in the manufacturing, testing, packaging or labeling of Ibritumomab Tiuxetan, the kits, or Yttrium-90 Chloride Sterile Solution, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval consistent with 21 CFR 601.12.

As requested in your letter of October 9, 2001, marketing approval of this product for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma, other than those patients with Rituximab-refractory, follicular NHL, is granted under the accelerated approval for biological products regulations, 21 CFR 601.40-46. These regulations permit the use of certain surrogate endpoints or an effect on a clinical endpoint other than survival or irreversible morbidity as bases for approval of products intended for serious or life-threatening illnesses or conditions.

Approval under these regulations requires that you conduct adequate and well-controlled studies to verify and describe the clinical benefit attributable to this product and that such studies be carried out with due diligence. If the postmarketing studies fail to verify that clinical benefit is conferred by Ibritumomab Tiuxetan, or the clinical studies are not conducted with due diligence, the Agency may, following a hearing, withdraw or modify approval to the extent that approval rests on the surrogate endpoint data.

Granting of this approval is contingent upon completion of clinical studies, as outlined in your commitment of December 12, 2001, designed to do the following:

1. To verify the clinical benefit and further assess the safety and efficacy of Zevalin radioimmunotherapy in patients with chemotherapy relapsed or refractory follicular non-Hodgkin's lymphoma (NHL). This will be assessed in a randomized, multicenter study to establish the net clinical benefit of the Zevalin therapeutic regimen used in combination with Rituxan as compared to Rituxan therapy alone. For this study, the primary efficacy variable will be event-free survival defined as absence of disease progression, initiation of additional lymphoma therapy, or death from any cause. Uniform criteria will be used to define when additional anti-lymphoma treatment is initiated including the presence of disease-related symptoms, threatened end-organ

function, cytopenias secondary to NHL, massive bulk disease, or steady disease progression over at least 6 months without meeting the definition of progressive disease. The final protocol will be submitted to CBER by May 30, 2002. Completion of subject accrual and the study are anticipated by November 30, 2004 and May 30, 2006, respectively. A final clinical study report will be submitted to CBER by August 30, 2006.

2. To verify the clinical benefit and further assess the safety and efficacy of the Zevalin therapeutic regimen in patients with transformed CD20+ B-cell NHL. For this study, the primary efficacy variables will be overall response rate and duration of response. Other measures of clinical benefit will include event-free survival, time to progression, and quality of life and disease-related symptoms, including B symptoms. The final protocol will be submitted to CBER by May 30, 2002. Completion of subject accrual and the study are anticipated by November 30, 2004 and November 30, 2005, respectively. A final clinical study report will be submitted to CBER by February 28, 2006.

3. To continue to assess patients enrolled in Study 106-04 and 106-06 for progression-free (PFS) and overall survival (OS). Patient follow-up data will be collected every 6 months, until the time to progression data has matured. The first of these data assessments will be submitted to the IND by May 30, 2002. An addendum to the 106-04 and 106-06 final study reports providing the results of comparative analyses of PFS and OS will be submitted to CBER three months after the final analysis. The projected date for the final clinical report to be submitted to CBER is November 30, 2002.

Design, initiation, accrual, completion, and reporting of these studies are expected to occur within the framework described in your letter of December 12, 2001. It is understood that, to fulfill the requirements of accelerated approval, the above studies must be appropriately designed and conducted with due diligence and must demonstrate clinical benefit.

In addition, we acknowledge the following agreed upon post-approval commitments, as described in your letters of December 12, December 18 and December 20, 2001 and February 14, 2002:

4. To continue assessment of the immunogenicity of the Zevalin therapeutic regimen by long-term monitoring for human anti-chimeric and human anti-murine antibody response in subjects enrolled in all Zevalin studies under any IDEC-sponsored IND including the post-approval commitment studies listed under items 1 and 2 of this letter. Interim data on immunogenicity will be submitted annually to the IND(s) and a final report will be submitted by August 30, 2006.

5. To continue long-term monitoring of subjects to determine the incidence of myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML). This monitoring will be conducted in all Zevalin studies under any IDEC-sponsored IND,

including the post-approval commitment studies listed under items 1 and 2 of this letter. Interim data on MDS and AML will be submitted annually to the IND(s) and a final report will be submitted by August 30, 2006.

6. To perform a suitable extraction study with the Ibritumomab bulk in the 1L polycarbonate container, as described in your response to the Agency's pre-approval inspectional observations. The study will be completed by June 30, 2002 and the results submitted to CBER in the next annual report.

It is requested that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). All adverse experience reports should be prominently identified according to 21 CFR 600.80 and be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

You are required to submit reports of biological product deviations in accordance with 21 CFR 600.14. All manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution, should be promptly identified and investigated. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, a report must be submitted on Form FDA-3486 to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 2567. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels).

As specified in 21 CFR 601.45, you are required to submit any promotional materials that contain information relating to an accelerated approval indication to CBER, for review and approval, at least 30 days prior to the initial publication of any advertisement or to the initial dissemination of any promotional labeling. You may also submit draft copies of proposed introductory advertising and promotional labeling that only contain information related to Zevalin for the treatment of Rituxan-refractory follicular, non-Hodgkin's lymphoma, for review. In addition, all final printed advertising and promotional labeling should be submitted at the time of initial dissemination. Promotional materials should be submitted with an FDA Form 2567 or Form 2253 to the Advertising and Promotional Labeling Branch, HFM-602, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other products should be made

unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Sincerely yours,

Jay P. Siegel, M.D., FACP
Director
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Exhibit G

Power of Attorney and General Authority
from Assignee

Power of Attorney and General Authority from Assignee;

Certificate Under 37 C.F.R. §3.73 (b)

Inventor: Darrell R. Anderson et al.

Patent No.: 5,776,456

Issued: July 7, 1998

For: **Therapeutic Application of Chimeric and Radiolabeled Antibodies to Human B Lymphocyte Restricted Differentiation Antigen For Treatment of B Cell Lymphoma**

IDEC Pharmaceuticals Corporation (IDEC), a Delaware corporation whose principal business address is 3033 Callan Road, San Diego, California 92121, hereby certifies that it is the assignee of the entire right, title and interest in the patent identified above by virtue of an Assignment executed by the inventors, recorded in the U.S. Patent and Trademark Office on December 4, 1995 at Reel 7735, Frame 0688.

The undersigned (whose title is supplied below) is empowered to act on behalf of the assignee.

The undersigned has reviewed all of the documents in the chain of title of the patent identified above and, to the best of undersigned's knowledge and belief, title is in the assignee identified above.

The assignee hereby appoints Robin L. Teskin, Reg. No. 35,030; Samir Elamrani, Reg. No. 43,601; Charles Rories, Reg. No. 43,381; and Michael Sanzo, Reg. No. 36,912, all registered to practice before the Patent and Trademark Office as its attorneys with full power of substitution and revocation to transact all business in the Patent and Trademark Office in connection with the above-identified patent, including, but not limited to, filing for patent term extension term 35 U.S.C. § 156. The assignee requests that all correspondence and telephone communications be

directed to the following person at the mailing address and telephone number hereafter given:

Name:	Robin L. Teskin
Registration No.:	35,030
Address:	Pillsbury Winthrop LLP 1600 Tysons Boulevard McLean, Virginia 22102
Telephone No.:	(703) 905-2200

The assignee further gives general authority to Robin L. Teskin, Samir Elamrani, Blair Taylor, Charles Rories, and Michael A. Sanzo to act on its behalf in patent matters. This includes the authority to make the declaration referred to in 37 C.F.R. § 1.740(b) and § 1.740.

The undersigned hereby declares that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the patent.

FOR: IDEC PHARMACEUTICALS CORPORATION

BY: 

Christopher Dayton

DATE: 4/16/02